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NATIONAL FORMULARY XIII

The National Formulary – Thirteenth Edition
(NF XIII)

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by authority of the
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PREFACE

Man has recognized the basic need for drug standards and specifications virtually since he first began to employ substances with purported medicinal properties in his attempt to alleviate illness and suffering. Most of the drugs which were available from prehistoric times until the dawn of the sulfa-antibiotic age were at best crude nostrums. Few of these articles did the patient any good, and he was probably fortunate if they did him no harm.

The state of drug standardization has followed a rather parallel course in its development and history. While efforts had been made to achieve means whereby medicinals could be examined and assessed as to their identity, purity, and potency, most of these efforts resulted in methods equally as crude and unreliable as the nostrums themselves.

However, almost coincident with the birth of the chemotherapeutic age, the science of analytical chemistry began to advance with enormous strides. Fortunately, pharmaceutical scientists recognized the potential application of these new and remarkable approaches to the analysis of drug substances and drug formulations. With ingenuity which rivals that seen in any field of science or technology, pharmaceutical scientists—particularly during the past ten years—have utilized the recent developments in analytical methodology in the testing of pharmaceuticals. The net result permits inspection of infinitely smaller samples, enormously greater selectivity, and drastically improved precision and accuracy.

The fundamental purpose of the National Formulary is to provide standards and specifications which can be used to evaluate the quality of pharmaceuticals so that the physician can prescribe drugs with assurance, the pharmacist can dispense drugs with reliability, and the patient can consume drugs with confidence.

Exhibiting a singleness of purpose, the entire efforts of the National Formulary Board—as well as the NF Committees, panels, individual advisors, and staff—during these past five years have been directed at providing just such standards and specifications for the benefit of the professions of medicine and pharmacy, and particularly in the interest of the general public. In pursuing this course, the many recent developments in drug analysis and related methodology have been freely drawn upon and widely utilized. While it will be left for history to determine the full impact which this new compendium will have on the future course of drug standardization, nevertheless, one prediction can be made with confidence: the new National Formulary provides a combination of the most advanced and authoritative means heretofore available for assessing drug quality. Never before has the pharmaceutical analyst, from a regulatory standpoint, been in the posture of being able to determine and ascertain so much regarding the identity, strength, quality, and purity of many of the drugs with which he is concerned.

Organization and Codification

The end product of any program or activity is generally greatly influenced and affected by the depth of planning and degree of organization which has been utilized in developing and executing that program or activity.

The content of the National Formulary has gradually evolved over the past 78 years from a simple drug recipe book to a highly sophisticated compendium of complex scientific information. During this same period, the distribution and use of the NF—earlier limited to a relatively small group of pharmacists—has grown so that it now reaches a large number of national and international users including members of all the health professions, as well as the pharmaceutical industry, pharmaceutical education, law enforcement agencies, and many others. It has come to be formally recognized as an official compendium of drug standards and specifications under terms of the federal as well as the state drug laws.

It is only natural that the mechanism whereby this compendium is revised and published has also become much more complex and intricate as these various aspects of growth, expansion, and maturity have taken place. Regrettably, before 1965 the formal codification of the present organization of the NF structure had not been accomplished. The full responsibilities of the various bodies within the organizational framework had not been officially stipulated nor defined. This was the case in spite of the fact that the need for such codification had been recognized for many years and was the primary point brought out in the 1959 Remington Address by the retiring NF Director, Justin L. Powers. He suggested that consideration be given to expanding the APhA By-Laws to describe the National Formulary operation in greater detail.

The need for this public clarification of the authority and responsibilities of the organizational units within the NF, as well as the overall function and purpose of the NF itself, now appeared to be even more urgent than ever before.

As a consequence, immediately after publication of NF XII in early 1965, efforts were initiated for a thorough reorganization of the entire committee and staff structures, the delineation of responsibilities, and in general, a formalization of the complete NF revision and publication process to render it highly methodical and systematic. This effort culminated in early 1967 with the adoption of revisions in the APhA Constitution to recognize the NF program as the first objective of the Association's existence, and the addition of an entire new APhA By-Laws chapter pertaining exclusively to the NF codification (the pertinent portions of the Constitution and By-Laws are reprinted beginning on page xlv). One particularly notable feature of the codification is the provision for an appeals route. This is just one facet of the codification which is designed to provide the National Formulary with a greatly enhanced legal foundation in the event of any challenge either to its basic authority, or its method of arriving at the specifications adopted, or the specific standards thereby derived.

The terminology used to designate various constituent NF groups was also changed in 1967, with probably the most significant change being the redefining of the group formerly identified as the Committee on National Formulary to the present National Formulary Board. This present term more clearly reflects the full responsibilities and broad functions of this body. It also facilitates the establishment of a more clearly related organizational framework of constituent committees (Admissions Committee and Specifications Committee), as well as advisory panels.

Furthermore, in an effort to present in a systematic and concise form the stepwise procedures entailed in the NF revision and publication program, highly detailed flow diagrams were prepared to provide this information in graphic stepwise fashion. The flow diagrams cover all the major phases of the NF program and are available for public reference.

Statement of General Principles

A critically important consideration during the early stages of each NF five-year revision period is the development of the statement of *General Principles* to be followed in the compilation of the new edition of the compendium. This statement summarizes the general policies adopted by the National Formulary Board and constitutes the guidelines utilized in subsequently planning and implementing the program for the revision and preparation of the NF. Many innovations of policy and procedure were initiated by the NF Board at the beginning of the revision period just concluded, with a view toward having the National Formulary fully meet current needs of drug standardization. Therefore, the statement of *General Principles* has required extensive change and expansion in order to reflect accurately the policies which have been formulated to guide all those persons having some responsibility in the mammoth task of preparing NF XIII. Following adoption by the NF Board, and after approval by the APhA Board of Trustees, the revised statement was made public and widely publicized through announcements in the pharmaceutical press. The statement, as adopted, appears beginning on page 1 of this volume.

Admissions Policy

A fundamental consideration which was carefully reviewed in depth by the National Formulary Board was the admissions policy to be employed for NF XIII. The NF Board unanimously and emphatically reaffirmed the policy adopted in 1961 and initially employed for NF XII—namely, that therapeutic value would serve as the sole criterion in considering articles to be admitted to the NF for medicinal purposes.

The Board also defined its policy with regard to the admission of drug combinations—namely, that NF monographs for combination dosage forms will be limited to those combinations for which there is a therapeutic advantage to the patient as contrasted with administration of the separate individual therapeutically-active ingredients.

On the other hand, a broader policy was adopted and followed relative to the admission of pharmaceutical aids or adjuncts by not limiting such admissions to those ingredients specified in NF monograph formulas (recipes). Pharmaceutical aids are utilized as excipients in preparing dosage forms but are generally without therapeutic value in themselves. Providing NF monographs for a broader group of such articles will serve to give greater assurance of quality and purity suitable for pharmaceutical purposes.

After careful consideration of the various factors and ramifications involved, the NF Board decided not to admit to NF XIII drugs which are used solely for veterinary purposes. As a consequence, all articles admitted to NF XIII are on the basis of their usefulness in human medicine or as adjuncts relating to human medicine.

Articles Admitted

Based upon the recommendations of the NF Committee on Admissions and its Subcommittee on Dosage Forms, over one thousand articles were provisionally admitted to NF XIII. Of these, suitable monographs were prepared for 992 articles which were accorded final admission to the new edition. A record-shattering 411 (or 41 percent) of these articles are being newly admitted to the National Formulary. At the same time, 221 drugs which had been in the previous NF are no longer accorded NF recognition.

In May 1967 the initial list of provisionally admitted drugs was released from the NF office simultaneously with the release of a similar list from the USP office. Because of the much greater interest in this information as a result of Medicare legislation and other reimbursement programs, a conscientious effort was made to coordinate the release of such information from the respective NF and USP offices, and to provide this information as early in the respective revision programs as possible.

The unusual character of the newly admitted articles also warrants comment. These newly recognized drugs fall into a broad range of therapeutic classes including various oral contraceptive agents (as well as the first such combination dosage forms to be officially recognized), the first prophylactic antiviral agent, cardiac drugs, diagnostic aids, hypoglycemics, tranquilizers, a broad array of potent steroids, and the first aerosol propellants (as well as the first aerosol dosage forms).

Pharmacological Category Statements

Beginning with NF X, published in 1955, brief statements have been appended to National Formulary monographs to indicate the principal pharmacologic or therapeutic property of the respective articles. While the terms used were generally accurate in themselves, there had been many inconsistencies and discrepancies when the terms used were compared for similar or related drugs.

The need for a uniform and systematic set of category statements has been recognized for some time. With the NF now placing emphasis on therapeutic value in considering drugs for admission, greater use is made of the category statements, such as in preparing lists of NF drugs grouped by pharmacologic properties. Another feature which has added considerably to the importance of the category statements is their use in connection with drug coding or with information documentation and retrieval systems. The information which is fed into a computer is often entered under the heading of the drug classification. Inconsistent classifications would lead to serious limitations or errors in such systems.

Consequently, a uniform set of NF category statements has been developed and approved by the NF Admissions Committee. The complete listing appears beginning on page lxvii.

Dose Statements

The reorganization of the pharmacological category statements to present this information in a more systematic fashion is one major change in NF XIII which is of interest to the practicing pharmacist or physician. As another example of this nature, the information provided in the individual monographs with respect to dosage has been substantially expanded. In many cases a *usual dose range* is now included in addition to the *usual dose* statement.

The dosage information given in the official compendia is regarded with a considerable degree of authority, despite the limitations spelled out in the NF General Principles (see page 3), and in the General Notices (see page 12). In light of this, it should be reemphasized that such dose information applies to normal adults, unless stated to the contrary.

Indeed, the NF Board studied the possibility of providing additional information for special segments of the population, but came to the following conclusions with respect to these special groups:

> *Infants and Children*—Generally, no doses are provided for infants and children because of the differences in their response to drugs which may result from many factors unique in the process of growth and development. An infant's or child's dose requires adjustment to his needs based upon a number of factors, including growth in size, maturity of organs and their functions, and in particular the maturity of processes related to drug metabolism.
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> *Pregnancy*—The Usual Dose statements provided in the NF do not apply to pregnant women. During pregnancy there are certain drugs which should not be used, and —for those drugs which are used— the doses must be carefully individualized since drugs, depending on their dose, may have temporary or permanent effects on the growing fetus.
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> *Aged Individuals*—Doses must be individualized in the aged because impaired ability to metabolize or excrete drugs, or other pathology, may cause abnormal responses to drugs.

Drug Quality

For many decades the medical and pharmaceutical professions had confidently relied upon the quality of the drugs which they respectively prescribed and dispensed. They had come to look to the official compendia as the cornerstones upon which such drug quality was firmly based. But history will record the latter half of this past decade as the period during which man everywhere began to ask questions and raise doubts about the most traditional and accepted facets of his environment and the systems which man himself had established. If religion, social behavior, and civil authority could be subjected to such fundamental reassessment, it is no wonder that searching questions and similar doubts arose concerning drug quality.

Regrettably, in this total picture the professions were simultaneously buffeted by other forces not the least of which included economics and political considerations.

Placing all this within a context where the scientific aspects were already somewhat dim and clouded, it is no wonder that the confidence of the practitioner in his reliance on the traditional pillars of the official compendia was noticeably shaken.

During this period, National Formulary officials attempted to provide both clarification and direction in the hotly debated area of drug quality:

> *Clarification*, by distinguishing between the establishment or existence of standards and the actual compliance with those standards; by distinguishing between the testing and data needed prior to marketing a new drug or drug product as contrasted to the testing and standards appropriate for subsequent batches of a drug product already marketed; by distinguishing between the ideal requirement that every batch of every drug be clinically tested in human subjects, and the pragmatic necessity of using specific physical, chemical, and biological tests carefully selected through scientific study and deduction.
>
> *Direction*, by organizing panels and fostering the study of factors bearing on drug quality, and subsequently—through the legislative framework inherent in the compendia—by establishing new tests, new specifications, and new standards, all designed as steps forward in the constant and continuing quest for drug quality.

The official compendia are not perfect instruments, and no claim has been made that they are. However, the fact remains that compendial standards constitute the best, if not the only, scientific yardsticks by which an objective measure or assessment can be made of the quality of a particular drug product.

Bio-availability

The official compendia have long set the pace in developing standards and establishing specifications for the identity, purity, and strength of drugs. Relatively recently, however, an awareness has developed that other properties can play a significant role from the standpoint of satisfactory quality of a particular drug product. These properties can affect what has come to be referred to as the "physiological availability," or the "biological availability," or the "bio-availability" of the drug product—in essence, the extent to which the active ingredient in a drug product can be taken up by the body in a form which is physiologically active.

In other words, even if the drug is of the highest purity, is it in a suitable physical state which lends itself to proper utilization in a biological system on the basis of its physical properties or conditions? Such factors might pertain to the polymorphic form of a crystal or to the particle size of any drug substance in the solid state. Such factors might also relate, in the case of dosage forms, to the buffer capacity and pH adjustment of an injectable or ophthalmic fluid, or the propensity to dissolve in the case of a tablet or capsule intended for oral administration.

Our full recognition of these problems—like that of the entire scientific community—is relatively recent. It follows, therefore, that our ability to resolve these problems has been limited by the scientific knowledge available, coupled with the simple fact that time is required to translate new knowledge into meaningful standards. However, the National Formulary has responded to these challenges with vigor and has recognized the inherent urgency of developing appropriate solutions.

As an important initial step, a USP-NF Joint Panel on Physiological Availability was appointed. The panel included individuals with wide experience in this area as well as a wide diversity of affiliations and viewpoints. The joint panel began its work by considering types of tests which might be valuable and useful as an indication of the physiological availability of a particular drug product. The panel then considered methodology for conducting such tests as well as the drug dosage forms to be given highest priority in the application of such a test. The findings and observations of this joint panel have been freely drawn upon by the NF Board in deciding the direction which is being taken relative to adoption of the new dissolution test for tablets and capsules and the manner in which this test is being specified in individual monographs.

The NF Board felt that, where indicated, it would be even more valuable to establish appropriate specifications both for the active ingredients, and the final dosage form, to serve as an index of drug quality from the standpoint of expected biological availability. In this manner, the problem would be subjected to a two-pronged attack.

Clinically, it has been demonstrated that crystal form can have a marked influence on the absorption profile of certain chemical substances which can occur as polymorphic forms in the solid state. A special NF panel was established and the new X-ray diffraction specification eventually resulted from the activities of this group.

As indicated above, the fact that the physical form of a drug or the physical characteristics of the dosage form in which it is administered can play a highly significant role in determining the biological suitability of that drug has only recently become recognized. Present-day pharmaceutical research is being concentrated on uncovering the relative importance of these factors and how they influence the performance which might be anticipated from the drug when it is administered. This research is actively in progress in many industrial, academic, government, and private laboratories. As quickly as information and conclusions become available, appropriate standards and specifications are being established by the official compendia in an effort to provide a means of assessing and ensuring drug quality from these standpoints. The X-ray diffraction specification and the new dissolution test for tablets and capsules constitute just two dramatic examples of the strides which have been made through the efforts of the NF Board to provide objective means of assessing drug quality with respect to drug form and formulation, as these attributes might influence the biological performance of the article.

Tests and Assays

The National Formulary, by law, establishes standards and specifications for the articles included therein. Almost of equal importance, however, are the procedures utilized in determining compliance. This fact became very evident to Congress and the federal agencies during the early part of this century. The 1906 Food and Drugs Act only required that articles comply with NF specifications but did not specify how compliance might be determined.

Unscrupulous operators seized upon this latitude to utilize faulty, imprecise, and crude methods which often gave results indicating whatever these operators set out to demonstrate. Congress closed this loop-hole in the 1938 Federal Food, Drug, and Cosmetic Act by stipulating that compliance must be demonstrated using the procedure given in the official compendium. This action served to add considerable importance to the test methods and procedures—as distinguished from the specifications and tolerances—adopted by the compendia.

A very significant indication of the progress made in utilizing the most advanced knowledge and sophisticated analytical techniques as applied to drug standards is evident from the new NF General Tests chapters. These new General Tests are extremely diverse in their nature as well as in their intended purpose. The diversity is evident from the following partial list of new chapters: Selenium Limit Test; Salmonella Test; Dissolution Test; Steroid Chromatographic Purity; Rubber Closures; Coulometry; Phase Solubility Analysis; and X-ray Diffraction. About 15 new chapters are being added to the General Tests section and all the chapters being carried over from NF XII have undergone revision, which in some cases was quite extensive. For example, the chapter on Spectrophotometry has been expanded to include atomic absorption spectrophotometry as well as fluorometry and nephelometry.

The establishment of methodology, as described in the preceding paragraph, now permits the application of such specifications or requirements within individual NF monographs where such a requirement is considered to be desirable or necessary. As an illustration, the new Salmonella Test now enables the NF Board to specify in pertinent monographs of drugs derived from animal sources that such articles be free from Salmonella. The chapter on X-ray Diffraction provides a technique enabling the NF Board to specify in those monographs where polymorphism or crystal form may be a potential problem that the article must conform to a specified X-ray diffraction pattern for it to be regarded as complying with the NF specifications. Consequently, appropriate requirements have been entered in the pertinent individual monographs to utilize as far as possible and practical the new General Tests procedures.

It was anticipated that a completely new General Tests chapter would be provided in NF XIII for Sterility Tests. While much effort was expended on this project by a panel under the direction of the USP, progress in this area did not proceed to the point where the NF Board felt that the proposed new procedures could be adopted with full confidence for inclusion in NF XIII. As a consequence, although a drastically revised version did appear in NF XIII galley proof, the version from NF XII was reinstated by way of page proof and now appears in this compendium.

Hopefully, the remaining questions about the proposed new Sterility Tests chapter can be resolved at an early date and the resulting new version will then be adopted by way of a Supplement to NF XIII. If this materializes, it is assumed that the membrane filtration technique will be a part of the new chapter. Moreover, adoption of the membrane filtration technique will enable the NF Board to specify a sterility requirement in the individual monographs for ophthalmic ointments as the Board had originally intended.

Aerosols

A new dosage form will be officially recognized for the first time in NF XIII through inclusion of several monographs for aerosol preparations. Heretofore, no aerosol had been recognized in the official compendia. This development has been made possible by the establishment of criteria concerning what basic requirements aerosol products should be required to meet. Depending upon individual cases, these might include leak testing, labeling requirements, total content of the container, quantity of drug delivered by a metered-dose valve, and so on. Furthermore, among the new monographs being admitted to NF XIII are several which provide standards and specifications for the principal propellants most commonly used for aerosol purposes.

Content Uniformity

A new type of test specification was applied for the first time in six NF XII tablet monographs. This specification is referred to as the "content uniformity" test, and it was adopted after long study on the basis of evidence indicating the need for such a requirement to demonstrate acceptable homogeneity of prepared tablets.

The National Formulary Board extended this specification to all NF XIII tablet monographs where (a) the active ingredient is present in relatively low quantities—usually 50 mg. or less of any strength available; and (b) test procedures and similar considerations indicate that it is feasible to apply the specification. Furthermore, this same concept has been extended in NF XIII as a test specification to other dosage forms where such a requirement is considered to be desirable and shown to be practical. These other dosage forms include capsules and sterile solids. As a consequence, this specification is widely employed in NF XIII monographs; the net effect is to provide greatly increased assurance of homogeneity from the standpoint of uniformity within a single lot.

Timed-Release Preparations Test

A test procedure, as well as the pertinent apparatus for conducting the test, for the *in vitro* examination of timed-release tablets and capsules was officially adopted by inclusion in the Second Supplement to NF XII. This new procedure—which is now formally incorporated in the NF XIII General Tests section—provides a useful means of establishing suitable test criteria to assure product uniformity of most timed-release preparations. The procedure is provided for its value as a routine control test method, and in order to foster uniformity and inter-laboratory consistency in conducting such testing.

A noteworthy feature of this action is that it represents some departure from usual compendia practice in that no specific product specifications are presently being established. Instead, adoption of this test procedure serves to provide general guidelines and direction in the development of acceptable procedures of drug testing and pharmaceutical analysis. This reflects an awareness on the part of the NF Board of its broadened responsibility in helping to assure appropriate drug standards in light of modern manufacturing and analytical techniques.

Automated Analysis

A growing awareness has developed that drug quality control testing by manufacturers, and drug quality enforcement testing by government agencies, must be increased even further to provide better assurance of a safe and effective drug supply. This view also is shared by the NF Board, and is reflected in many of the new tests and specifications. A particular case in point is the content uniformity test, since this specification is directed at determining uniformity *within* a given batch or lot, rather than simply uniformity *between* lots.

However, one major complaint has been raised concerning the greatly increased analytical load caused by the new test. Even though in certain instances a more simplified test procedure can be utilized in place of the regular monograph Assay, nevertheless the requirement that at least ten and as many as 30 separate individual replicates be performed is obviously burdensome and constitutes a greatly increased demand on facilities and personnel for the parties involved—whether in the laboratory of the manufacturer or in some enforcement agency such as the Food and Drug Administration.

As an unrelated but nonetheless parallel development, an entirely new dimension has been added to pharmaceutical analysis within the last five years. We have witnessed the successful application of the technology of automation to drug analysis.

Automated analytical equipment presents a means of saving both time and personnel, and ultimately equipment and costs. Unfortunately, the application of automated analysis to official compendium procedures is not without some difficulties.

The first problem encountered is the prohibition—under Section 501(b) of the Federal Food, Drug and Cosmetic Act—against the use of an analytical method different from that appearing in the NF.

The second problem is that of prohibition against alternative methods. This policy recognizes that the NF test and assay procedures must be the common ground between plaintiff and defendant—between enforcement agency and manufacturer. If compliance or lack of compliance could be shown by different methods, this would either place an undue burden of proof on the government or place the manufacturer in double jeopardy.

The third problem pertains to the obligation that NF procedures be general in nature, indicating that it would not be reasonable to require that everyone perform a particular procedure, such as the content uniformity test, using automated equipment.

In the face of these considerations, the NF Board gave the matter deep study with the hope of formulating a policy and interpretation which would at the same time fulfill pragmatic and practical aspects while still satisfying the legal obligations and responsibilities of the NF as an enforcement device.

The Board concluded that: (a) the NF only intends to state what shall be done and is silent on who or what shall perform the actions; (b) the NF only intends to recommend equipment which would be suitable (see initial paragraph under *Apparatus*, page 8); and (c) the NF does require that—in order to demonstrate compliance, or lack of compliance—the exact chain of chemical and physical steps must be conducted. This says that the integrity of the official procedure must be maintained in that a different analytical procedure cannot be used nor can significant steps be eliminated. There is no flexibility in this latter area.

To clarify beyond any doubt the Board's position in this regard, the General Notices have now been revised accordingly (see initial paragraph under *Procedures*, page 9).

Significance and Function

The National Formulary serves pharmacists and pharmaceutical manufacturers by providing standards for the procurement of drugs used in dispensing, prescription compounding, and manufacturing, and by supplying formulas and working directions for the preparation of some dosage forms. It provides standards for use by state and federal food and drug law officials in their enforcement programs, thus simplifying legal procedures.

The activities and functions of the National Formulary also constitute an important service to the medical profession and to the public. The first three editions of the National Formulary served mainly as a convenience to practicing pharmacists by providing uniform names, uniform formulas, and working directions for the small-scale manufacture of pharmaceutical preparations frequently prescribed by physicians.

Under the present criterion of *therapeutic value*, as described under the heading of *Admissions Policy*, the National Formulary has also assumed added importance as a therapeutic guide for pharmacists and physicians. Taken together, those articles which now appear in the concurrent editions of the National Formulary and the United States Pharmacopeia constitute the drugs of the greatest established merit and the most generally accepted usefulness.

Until 1906, when it was designated as one of the two official compendia by the terms of the Federal Food and Drugs Act, the function and significance of the National Formulary remained unchanged. The provisions inherent in the 1906 law and the Federal Food, Drug, and Cosmetic Act of 1938 and its amendments—particularly those enacted in 1962—have subsequently increased the obligation of those responsible for the revision of the National Formulary, and in turn, have added greatly to its significance.

The position of the National Formulary as a book of legal standards for drugs is made clear by the references to it in the 1938 Federal Food, Drug, and Cosmetic Act. Section 501(b) of this statute requires that drugs purporting to be those listed in the National Formulary must conform to the standards of strength, quality, and purity prescribed therein. All determinations of these standards must be made in accordance with the methods prescribed in the text. Variations from these standards are permitted only when certain labeling requirements of the Act indicating the nature of the deviation are met.

The same section of the Act authorizes the U.S. Secretary of Health, Education, and Welfare to prescribe tests where none have been provided or where those described are believed to be inadequate. Before the Secretary can take such action, however, he must first call to the attention of those responsible for the revision of the National Formulary the need for additional or more adequate tests. He may then proceed only after a reasonable period of time has elapsed, and if the National Formulary Board has failed to provide adequate tests or methods of assay. Thus, while considerable recognition of NF standards is shown in the Act, adequate checks and safeguards against omissions and arbitrary or scientifically unsound specifications are also provided.

Nomenclature

The last edition of the National Formulary was published at a time when drug nomenclature was an extremely controversial and troublesome topic. By "nomenclature" is meant simply the selection and agreement on suitable nonproprietary drug names, without any consideration here of trademark or brand names.

Indeed, the *Preface* to NF XII stated that "in recent years, probably no other single subject pertaining to drugs has received more attention from Congress, enforcement agencies, purchasing departments, hospitals, manufacturers, physicians, pharmacists, and the general public...." That *Preface* then went on to devote more space to this topic than any other subject discussed.

As amended in late 1962, the Federal Food, Drug, and Cosmetic Act contains certain provisions regarding drug names. The law refers to "established names" for drugs and defines such names to include the names given for dugs in the official compendia. Among the provisions embodied in the law are statements concerning "unduly complex names" and "simple and useful names." Authorization also is extended to the Secretary of HEW to review the NF drug names and to modify those names under certain specified conditions.

Early during this past revision period, the NF conducted a full-scale review to determine which NF drug names might possibly be regarded as being unduly complex, and to study what might be done of its own volition in the way of suitably modifying those names. Assistance in this project was provided by the USAN Council staff. Such reviews are highly complex and involved. Furthermore, when a decision is ultimately reached to make a name change, the process of transition is, at least temporarily, a traumatic one for all those affected by it. Consequently, such decisions are not arrived at lightly and often involve extended deliberation.

After extensive deliberation and consideration, the NF Board completed its review of NF monograph titles from the standpoint of their "usefulness and simplicity." On this basis, a number of monograph titles have been changed in going to NF XIII. The changes involved include two antibiotics, which present peculiar legal problems because of the distinctive requirements regarding certification of antibiotics embodied in the federal law. Through extensive negotiations, a mutually agreed upon procedure was developed with the FDA to achieve these name changes in an orderly manner and with a minimum of disruption and possible confusion. One of the contemplated name changes was the subject of an appeal to the APhA Board of Trustees, as provided for under the By-Laws. The appeal was rejected and the action proposed by the NF Board was upheld.

The APhA, through the participation of the National Formulary, continues to cosponsor the USAN Council—an activity in which it has formally participated since January 1964. The other two sponsors are the American Medical Association and the United States Pharmacopeia. For some time a mechanism had been sought to enable the FDA to participate in the USAN Council activities without violating the independent nature of the USAN Council and without compromising the FDA responsibilities under the law.

The need for such an arrangement became especially apparent in 1966 when the FDA published a proposal to adopt a certain non-USAN name, when a USAN name considered more desirable had been in use for a number of years. After considerable effort—especially on the part of the National Formulary—the FDA was dissuaded from its intended action and withdrew the proposal.

Subsequently, in June 1967, the USAN Council was reorganized on the basis of certain agreements concluded with the FDA. This reorganization serves to strengthen the USAN Council and to add additional stature to its decisions. The FDA took specific note of this in a statement which was published in the Federal Register on March 20, 1968, concerning general policy in regard to established names for drugs and regarding the processing of New Drug Applications. Later, the NF Director was appointed as one of three special consultants to the FDA Commissioner in the area of drug nomenclature. This appointment has served to maintain improved liaison and communication between the NF and the FDA in this important area.

While not strictly related to nomenclature, a comment would be in order here concerning chemical names and formulae. Current NF policy is delineated in the statement of *General Principles* (see page 1). It also should be mentioned that the chemical names and graphic structures portray the compounds only to the extent that their structures are actually known and have been fully verified. However, paticularly in the case of certain steroids, recent information from research laboratories indicates that various articles, previously regarded as being single isomers, are in fact composites consisting principally of the form represented, along with lesser proportions of other isomers. In viewing the chemical names and graphic structures, this possibility should be kept in mind; it simply reemphasizes the often stated admonition that one must always evaluate the total monograph and never appraise only a single feature or selected portion taken out of the full monograph context.

Drug Standards Laboratory

The official compendia have need for some direct laboratory assistance despite the very considerable time and talent contributed by the various Board members and other individual participants, as well as government, academic, and industry laboratories.

As noted in the *History* (see page xlii), the Drug Standards Laboratory was reorganized under the APhA Foundation in 1962. By the close of the NF XII revision period, the Laboratory was making a significant contribution to the NF program. Nevertheless, it remained quite apparent that the needs of the compendia required that much more be provided in the way of such assistance and service.

Consequently, by early 1968 the sponsoring organizations of the Laboratory (the American Medical Association, the APhA, and the USP) thoroughly reevaluated its function and role. A major extension of the Laboratory program and staff was embarked upon as a result of this reevaluation. The extension in program and expansion of staff has taken place during the past two years with the result that the Laboratory made a major contribution to the NF revision program by providing extensive laboratory assistance. The Laboratory now serves a most vital role as an integral part of the facilities which are drawn upon and utilized in the NF program.

HEW Task Force

During the past five years, government interest in expanding its drug programs to additional segments of the American public has stimulated some rather extensive—if not comprehensive—reviews and studies of related factors pertaining to drugs. Probably the most extensive of these studies, and the one which covered the broadest array of drug related topics, was the study made by the Task Force on Prescription Drugs of the U.S. Department of Health, Education, and Welfare.

National Formulary officials supplied technical advice and scientific consultation to the HEW Task Force in a number of subject areas, including: (a) pharmaceutical nomenclature; (b) drug coding and classification; (c) therapeutic classification; and (d) drug quality and quality standards.

Reference Standards

As noted in the historical commentary regarding NF XII (see page xli), the use of and need for reference substances for comparative testing purposes has literally mushroomed. This has been due primarily to the general use of instrumentation in compendial procedures. However, the program of supplying reference substances has also expanded due to other factors all of which reflect an awareness on the part of the NF Board that—even aside from their use in connection with procedures embodied in the compendium—this program in itself constitutes a very significant facet in the establishment of specifications when viewed in broad perspective.

Approximately 250 NF Reference Standards are now called for in tests and assays described in NF XIII. Of these, only about 70 had been previously needed, and therefore supplied by the National Formulary office.

Some of the new Reference Standards pertain to drugs previously recognized in the NF and which have been readmitted to NF XIII. Formerly, it was the NF policy to permit comparative tests to be conducted using a sample of the drug conforming to the pertinent NF monograph of the drug entity. As a result, a sizable number of NF dosage form monographs specified use of the drug substance rather than the corresponding NF Reference Standard. The NF Board concluded that it would be preferable to make available for distribution NF Reference Standards in each such case.

As a service to the pharmaceutical and scientific communities, a broadened program has been developed to supply, on order, other standardized substances which appear to be needed for pharmaceutical analysis or related purposes, even though these standardized substances are not required for tests or assays in the NF. To date this extended program includes: (a) standards for several articles formerly recognized in the NF; (b) standards for nearly a dozen antibiotics which are now subject to FDA certification; (c) five standards required by the Food Chemicals Codex and distributed under an agreement with the National Academy of Sciences; and (d) a standard for papain resulting from a direct request from the Pharmaceutical Manufacturers Association for establishment of such a standard.

The NF Board also established a new general policy, which has been implemented in NF XIII, that wherever there are NF Reference Standards available, the NF monograph for the corresponding drug substance will routinely include tests of infrared and ultraviolet spectra, unless there is a specific reason for making an exception. This serves to utilize the Reference Standards more fully in meaningful tests of an article's identity, purity, and quality.

Finally, in keeping with the growth and expansion of the Reference Standards program, a systematic protocol has been established and approved by the NF Board regarding the development, testing review, and approval of all new and all replacement NF Reference Standards. This protocol has been followed in developing all the new Reference Standards for NF XIII.

General Information

As an adjunct to its principal role of establishing drug standards and specifications, the National Formulary also serves in various auxiliary capacities. Being a convenient source of reference information to pharmacists, physicians, and others, constitutes one of these functions. The majority of the features which had been incorporated as matters of information in NF XII have been continued in the current edition. In most cases this required considerable revision of the material in order to update it in light of recent developments. For example, the General Information chapter on the International Pharmacopoeia required complete revision since not only are the comparisons made with NF XIII drugs (rather than NF XII drugs), but the Second Edition of the I.Ph. was issued in 1967, necessitating the revamping of all the comparative entries.

A major new chapter has been added to the General Information section. This is a Table of approximate solubility data, tabulating all such data which could be compiled in the NF office from various sources of information. While every effort was put forth to make the data in the table as accurate as possible, some discrepancies were noted in those values which appear in the literature or were obtained from other sources. This would indicate that—depending upon the source of information utilized—certain differences might be observed in comparing any literature value to what appears in the new Table. Of possibly greater disappointment, however, was inability on the part of the NF staff to obtain quantitative data from any available source concerning many of the NF articles, or at most, only very limited information pertaining to many others.

Several chapters which had appeared in the NF XII section have been deleted. Most missed will probably be the Synopsis of Federal Regulations for Narcotic Drugs; this chapter was dropped because all legislative signs pointed toward Congress enacting a new "omnibus" narcotic and dangerous drug law which would have rendered the NF chapter obsolete and inaccurate; while prompt passage of such a bill had been anticipated, no such new law had been passed at the time of this writing. The Optical Crystallographic Characteristics chapter also has been dropped due to inability to provide pertinent data for the many new drugs admitted to NF XIII in time for inclusion in the volume; it is hoped that this information can be compiled for inclusion of the chapter in an early Supplement. The listing of recipes for Podiatry Preparations was dropped in line with the therapeutic value criterion adopted for the entire National Formulary; it was concluded that the interests of podiatry—like general medicine, medical specialties, and dentistry—are best served by ensuring that drugs of importance in the practice of podiatry are included in the regular monographs section, and that the customary requisites of safety and demonstrated effectiveness be required as with all other medicinal articles.

While containing certain material which constitutes specifications and standards, the chapter on Pharmaceutical Preparations, which appears in the General Tests section, is largely informational in nature. The discussions of many of these dosage forms have undergone extensive revision, and several additional dosage forms are now covered for the first time as the result of new commentaries which have been introduced.

NF Style Book

The nature of the National Formulary as a legally recognized compendium of drug standards necessitates that particular care and attention be devoted to the uniformity of terminology and the clarity of expression employed in preparing the NF text. Since over 500 individuals actively participate to some degree in the revision program, it is necessary to ensure wide availability of the matters of style and interpretation of terminology which are utilized in the NF.

A style book, jointly published by the NF and the USP, previously provided such information to those serving the official compendia. However, the substantial editorial differences between the two books which later developed made it highly desirable to provide separate style publications. On this basis, a style book devoted exclusively to the requirements of the National Formulary was prepared and made available during the summer of 1966 for general use by those working on the revision leading to NF XIII.

This 52-page booklet spells out the specific details of format and editorial style to be followed in drafting text for inclusion in the National Formulary. Devoted solely to the requirements of this compendium, it proved to be exceedingly useful as the revision period progressed. The NF is a type of legal document, by virtue of its recognition in federal and state laws. Like most laws, the text of the NF is subject to interpretation by those whom it regulates as well as by the courts. Consequently, the text of the National Formulary must be clear, uniform, and unequivocal at all times, in spite of the fact that numerous individuals participate in the compilation of each new edition. Hence, the necessity of a detailed style manual is obvious.

Copies of this Style Book were distributed extensively to facilitate the appropriate wording of material drafted for inclusion in NF XIII by members of the NF Board, committees, and panels, as well as by various other participants who collaborated in the NF program. A supplement (1968) to the Style Book also was prepared and distributed in order to update the Style Book in light of changes in NF policy which were recently adopted by the NF Board.

Revision Processes

The revision processes relating to the preparation of NF XII had been materially expanded. These processes were further broadened during the past revision period in an effort to place the entire National Formulary program on the most democratic footing and authoritative foundation which it was possible to create within the prevailing bounds of personnel, time, and funds available.

Distribution of galley proof was increased to almost 300 interested persons. Moreover, page proof was circulated to over 200 proofreaders for comment, criticism, and correction.

Initiating an entirely new practice, beginning in 1966, an open discussion period has been held during the APhA Annual Meeting each year. This informal event is intended to provide appropriate opportunity for any interested person to discuss the NF Director's annual report, as well as any other aspect of the NF program, with the NF officers or Board members who are present.

A formal open conference on NF XIII page proof was held on August 14, 1969, in order to provide a final opportunity and public hearing for the registering of comments and recommendations in connection with the proposed content of the new National Formulary.

Format and Style

Although the two-column format used in NF XI and NF XII has been very well received, it had the minor disadvantage of subjugating the monograph titles and graphic material. In an effort to retain the desirable features of the two-column format and yet overcome this disadvantage, the format for NF XIII in the monographs section has been modified to present the titles and preliminary information—graphic structure, systematic chemical name, molecular formula, and molecular weight—in single-column form; that is, full-page width. Moreover, the monograph definition is the single most important part of any monograph and it is presented in indented fashion, and centered, to set it off from the rest of the monograph.

Previous efforts to distinguish between drug entities and dosage forms by use of different type designations presented repeated difficulties and unavoidable inconsistencies. As a consequence, no such effort at distinction is made in NF XIII.

Because it is standard practice in the National Formulary to list all monographs alphabetically according to the first noun or noun form in the title, there has been little need for cross references. However, it was recognized that combination dosage forms may be listed according to the different component ingredients, and that in the case of organic salts of cations, either the cation or organic anion might be given first. Hence, in these cases, italicized side headings have been introduced in the monographs section to cross-index pertinent page numbers.

Interim Revision

The need for continuously refining specifications and updating standards has become increasingly urgent. This development has been a natural consequence of the introduction of many new drugs and the accelerated growth of our knowledge concerning the pharmaceutical sciences.

In order to keep the National Formulary abreast of these developments and to maintain its standards as current as practicable, the NF Board from time to time issues Interim Revision Announcements and Supplements.

Interim Revision Announcements to

this edition of the National Formulary may be issued in the form of releases to the pharmaceutical press. Such Announcements are designed to publicize promptly minor corrections and other revisions of limited scope. Reprints of Interim Revision Announcements will be made available only upon request accompanied by an addressed and stamped envelope.

Supplements to NF XIII, covering a wider scope than can be included adequately in Interim Revision Announcements, will also be issued when necessary. Interim Revision Announcements published prior to the issuance of a Supplement will be incorporated in the Supplement.

Supplements, when issued, will be published and their availability publicized as described in the preceding paragraph. Copies will be mailed automatically, without cost, to every owner of a National Formulary XIII who takes the precaution to fill in and mail the "order form" postal card which is included inside the back cover of each book.

It is anticipated that Supplements to NF XIII will be issued with even greater frequency than for past editions of the NF, in an effort to place the NF revision program on a more continuous basis.

Indication of Patent Status

National Formulary drugs covered by patents—or for which patents are pending—are indicated by footnotes in the monographs concerned. This designation, as far as it was possible to determine, applies to patents in effect at the time of publication of NF XIII.

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A coupon will be found on the back of the title page, bearing the number of the copy and the following words: "National Formulary, Thirteenth Edition, Official Copy. Copyright, 1970, by the American Pharmaceutical Association." This coupon serves to identify an official copy of the National Formulary and should not be removed.

Recognition and Appreciation

The sheer magnitude and breadth of the program of activities necessary to develop a comprehensive new compendium of sophisticated methodology and complex standards requires the direct assistance and cooperation of literally hundreds of persons who serve on the NF Board, committees, and panels; as NF proofreaders; and as individuals simply interested in helping a cause they consider to be important. Only the NF Director is fully aware of, or can fully appreciate, the great personal efforts and sacrifice all these participants make on a voluntary basis, without compensation, and generally with the most meager personal recognition.

Even though a sincere effort has been made to list the names of all participants in various rosters and listings which appear in the preliminary pages of this new edition, and even though a few comments might be made here concerning the particular contributions of certain individuals or groups, mere words utterly fail to convey either the magnitude or the significance of the assistance they have provided. We can only hope that they glean personal satisfaction from the knowledge that through these efforts they have materially advanced the public health and welfare.

The reader is initially referred to page v on which appears the names of the National Formulary Board members. As provided in the By-Laws, the NF Board is charged with the primary responsibility for the revision and preparation of this compendium. Consequently, the greatest credit for each new edition must go to the pertinent Board. However, in our opinion, the current NF Board—both collectively and individually—did such an outstanding job of performing the task assigned to it that we cannot help but feel that their degree of participation and effort expended must be truly unique in the annals of volunteer service. It is also our conviction that the net result of the Board's effort—namely, the National Formulary, Thirteenth Edition—in itself reflects the success of this effort better than any verbal tribute or accolade.

The vast scope of the National Formulary requires a very considerable degree of specialized assistance in various diverse areas. The knowledge and talents of many persons have been freely drawn upon to satisfy this need. The two principal NF committees—the Committee on Admissions and the Committee on Specifications—provide the greatest source of such talent. These Committees, or panels drawn from them, have provided considerable assistance by conducting reviews and evaluations or performing other tasks in various specific areas.

Moreover, when a certain project has posed more than the usual problems, it has been the general practice to constitute a special advisory panel to study the matter in depth, and hopefully then to recommend a solution to it. Just one such example is the Advisory Panel on Chemical Names and Formulas which, under the able chairmanship of Dr. Clarence T. Van Meter, had responsibility for reviewing all the graphic structures, molecular formulas, and systematic chemical names, and then for revising them in accord with the latest reference sources recognized as most authoritative by the National Formulary. The rosters of most of these special advisory panels are provided immediately following the lists of the two NF committees.

There are many other instances where persons have provided the National Formulary program with help and assistance on an individual basis without being formally involved as members of the Board, committees, or panels. Insofar as has been possible, the names of these persons are listed as other participants, beginning on page xv. This National Formulary has benefited from valuable advice and cooperation from many collaborators, who voluntarily contributed of themselves, and who furnished information and recommendations which were considered in preparing the NF text.

The value and benefit of all this expert knowledge and assistance would have been largely dissipated or lost were it not for a loyal, efficient, dedicated, and diligent staff. As in the case of any great army in the field, effectiveness of operation and ultimate accomplishment is entirely dependent upon the availability and performance of supportive forces. In essence, the NF staff serves a similar function. Moreover, the NF office is the focal point for the many activities which are underway relating to the NF program in various laboratories throughout the United States and even abroad. Furthermore, the staff in the NF office coordinates and channels the operation of all the various NF boards, committees, and panels.

The Director of the National Formulary has had the benefit of this dedicated and loyal staff, the members of which compensated for their limited number by extending themselves on many occasions far beyond the call of normal duty.

Mr. Durward F. Dodgen, as Assistant Director of the NF for most of the revision period, was the immediate associate of the Director and he played a major role in seeing that the many phases of the program proceeded satisfactorily. The Director frequently called upon Mr. Dodgen to handle various matters on his behalf and in the name of the National Formulary. Because of his constant capable assistance, the Director wishes especially to single him out for the highest recognition and deepest appreciation.

As Mr. Dodgen's predecessor, Dr. Samuel W. Goldstein was very instrumental in helping the Director to get this past revision period off to a fine start. He also helped substantially in orienting his successor which maintained a smooth operation within the NF office. Dr. Goldstein's long association with the National Formulary has been extremely useful and beneficial; his unfailing devotion to all his various responsibilities has been a source of inspiration to all who know him.

Mrs. Rhea L. Talley coordinated many of the technical activities which took place behind the scenes, but were essential to the total NF operation. For example, few knew of her work in coordinating the reference standards program, in compiling background information for the Committee on Admissions, and in organizing all material for the printer.

Miss Linda LaFontaine joined the staff late in the revision period, but even in the relatively brief time prior to publication of NF XIII, she contributed significantly to its successful completion.

Mrs. Maria E. Cassidy, Miss Vivienne T. Chin, Mrs. Robbie E. Gupta, Mrs. Patricia A. Lefler, Mrs. Marie E. Lindsay, Mrs. Patricia A. Morrison, Mrs. Roberta B. Weissman, and the late Mrs. Clare H. Gee all contributed materially in processing correspondence and performing various secretarial duties relative to the NF revision and publication program.

The support provided by the APhA Board of Trustees, and in particular Dr. William S. Apple, the APhA Executive Director, to the NF Board and to the NF Director, was extremely gratifying. While the Board of Trustees and its Publications Committee have continually shown constructive interest in the National Formulary, the NF Director wishes to take especial note of the fact that at no time during his tenure has there ever been the slightest suggestion of interference with the NF operation, or even question of actions taken by the NF Board. This implies a degree of confidence on the part of the Board of Trustees and the APhA Executive Director which is appreciated and provides a source of deep satisfaction.

In setting specifications and standards which will be enforced by government agencies—in particular the FDA—and which must be complied with by the pharmaceutical industry, the NF of necessity has frequent contacts with personnel in those government agencies and in industry.

We are deeply pleased that, particularly during a time when similar relationships have been subject to stresses and strains for other than scientific reasons, the NF has maintained the most cordial relationships with the scientific and professional communities within both government and industry.

Personnel at the FDA have been of immeasurable assistance. The names of many FDA staff members will be found among the panels and other participants in the front pages of this volume; however, we would be remiss if we did not single out Dr. Daniel Banes, Mr. Jonas Carol, and Mr. James B. Kottemann for special mention due to their particularly great involvement with the NF program.

Many organizations within the pharmaceutical industry provide technical help and assistance to the National Formulary. None, however, exceeds nor equals the contributions made by the Quality Control Section of the Pharmaceutical Manufacturers Association in helping in the development of suitable and meaningful standards for drugs. Many of the official general procedures are the fruit of collaborative efforts which were initiated within this group. A debt of gratitude is hereby acknowledged; we also take this opportunity to note with pleasure the cordial relationship which the NF Director has enjoyed with the present and past officers of the Quality Control Section.

As noted earlier in this *Preface*, the Drug Standards Laboratory has played a most significant role in the successful completion of the NF revision program. The dynamic activity of the Laboratory is a direct reflection of the inspiration of

Mr. William J. Mader, Director of the Laboratory. His considerable assistance, as well as that of past and present Drug Standards Laboratory staff members, is gratefully noted.

The long existent, cordial relationships with the American Medical Association, and in particular its Department of Drugs and the USAN Council office—as well as the American Dental Association, and in particular its Council on Dental Therapeutics—have continued during this recent revision period. These relationships serve to emphasize the deep, if often unconscious, involvement of the other health professions in the matter of providing quality standards for drugs.

The NF and USP are often thought of as companion volumes, and in the manner in which they complement each other, they are indeed that. Their mutual aims and ultimate similarity of purpose naturally serve to bring them together, as well as to necessitate frequent contact and a close working relationship between their respective staffs. The cooperation provided by the USP staff in this connection—and particularly that of Dr. Lloyd C. Miller, USP Director of Revision—is gratefully acknowledged.

The Mack Printing Company has been selected to print all the recent editions of the National Formulary, and this firm again was chosen to print NF XIII. The efforts put forth by the staff at Mack Printing Company in various phases of the processing and production have been most commendable. The burden of coordinating the entire project resided with Mr. Charles B. Cowling, and through him we acknowledge the assistance of all his associates at Mack Printing Company.

Finally, the Director wishes to take particular note of the appointment of Dr. John V. Bergen to the NF staff as Associate Director of the National Formulary. This appointment is of special significance since Dr. Bergen is scheduled to assume the position of Director, effective January 1, 1970. At that time he will also succeed the incumbent as Chairman of the NF Board. The major contribution he has made during the completion of the NF XIII program, as well as his clear insight into the ramifications and complexities of the NF program, have clearly demonstrated that in the coming years the National Formulary will continue to go forward under his inspired leadership.

The completion of this compendium, therefore, also signals the termination of this writer's immediate involvement with the National Formulary and its program of establishing standards of quality for drugs intended for the prevention or cure of disease or the mitigation of suffering. We take this opportunity to thank all of those who responded to our call for assistance in this crusade, and we hope that in the years to come history will judge with favor the results of our efforts.

September 1969

2215 Constitution Avenue, N.W.
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HISTORY
# of the National Formulary*

Formularies and pharmacopeias from very early times have had an important and significant influence upon the establishment and observance of drug standards. The early standards for drugs, however, were not all comparable to those of today. That could not be expected. Standards for drugs of any period are always limited by the stage of development of the collateral sciences upon which they depend. The development of new standards for established drugs, and the discovery of new drugs, have closely paralleled the advancements in science. On the other hand, the search for a better knowledge of drugs has frequently contributed to the advance of science in general, and to pharmacy, chemistry, and pharmacology in particular.

Early pharmacopeias and formularies could do little more than provide uniformity of titles for botanical drugs and the few available medicinal chemicals, methods for preparation of the latter, and uniformity of formulas for dosage forms of these drugs.

The events leading to the publication of the first edition of the National Formulary and its progress since its appearance in 1888 illustrate a phase in the evolution of drug standards. When the American Pharmaceutical Association was organized in 1852, the only authoritative and generally recognized book of drug standards available was the third revision of the United States Pharmacopeia. It had been started in 1820 by physicians to serve as "a therapeutic guide to the medical profession." As such, its scope, then as now, was restricted to drugs selected by representatives of the medical profession, and believed by them to possess the greatest therapeutic merit. This selectivity has always prevented inclusion by the United States Pharmacopeia of a large number of drugs which enjoy a substantial degree of acceptance by physicians and are judged to have significant therapeutic value. This pharmacopeial selectivity is largely responsible for the origin and development of the National Formulary, and is one of the main reasons there are these two official drug compendia in the United States today.

The idea of a National Formulary for use in the United States is nearly as old as the American Pharmaceutical Association. This association of pharmacists organized in 1852 included among its original objectives the following:

"(a) To improve and regulate the drug market by preventing the importation of inferior, adulterated or deteriorated drugs and by detecting and exposing home adulterations. (b) To improve the science and art of pharmacy by diffusing scientific knowledge among pharmacists and druggists, fostering pharmaceutical literature, developing talent, stimulating discovery and invention, encouraging home production and manufacture in the several departments of the drug business. (c) To uphold standards of authority in the education, theory, and practice of pharmacy. (d) To create and maintain a standard of professional honesty equal to the amount of our professional knowledge with a view to the highest good and greatest protection to the public."

One means of partially activating these objectives was to promote the standardization of names and formulas for extensively used dosage forms of drugs not described in the US Pharmacopeia. It is therefore not surprising to find that as early as 1856 an American Pharmaceutical Association committee was appointed to develop plans for the compilation of standards for dosage forms not included in the United States Pharmacopeia of that period. During several ensuing years such a committee was continued, but plans for a formulary entirely acceptable to the Association were not presented. In the meantime, a book on elixirs by John Uri Lloyd, and the New York and Brooklyn Formulary for local use were published in 1883. Pharmaceutical interest in these books stimulated the Association to intensify its efforts to produce a formulary, and in 1888 the first edition of the National Formulary was published under the title "National Formulary of Unofficial Preparations."

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* For a more detailed history of early editions of the National Formulary see NF VII pages xiv to xxvii.

The designation "Unofficial Preparations" in the title was used because the Pharmacopeia had earlier adopted the term "official" as applying to the drugs for which it provided standards. The title of the publication was changed to "National Formulary" when, by the terms of the Federal Food and Drugs Law of 1906, both the United States Pharmacopeia and the National Formulary were designated as official compendia.

The First Three Editions of the National Formulary

The first edition of the National Formulary was a book of formulas for widely used dosage forms of that period such as elixirs, emulsions, fluidextracts, tinctures, solutions, syrups, and many others. At the time of its publication, there were no federal or state food and drug laws requiring adherence to National Formulary standards of nomenclature and composition of dosage forms. Despite the lack of legal compulsion, the National Formulary—like the United States Pharmacopeia—did much to promote uniformity in many drugs and preparations distributed under distinctive names. When the Federal Food and Drugs Act was passed in 1906, the National Formulary was well established, and it was natural that its standards should be recognized by the terms of that Act as those with which drugs described therein must comply. New editions representing minor revisions were published in 1896 and in 1906.

The Fourth and Fifth Editions of the National Formulary

A fourth edition, the first after the passage of the 1906 Federal Food and Drugs Law, was published in 1916. This edition marked a turning point in the scope of the National Formulary, and established a pattern for its future policies which has resulted in its development into a book of modern standards for drugs.

In the 1916 edition, standards of identity, strength, quality, and purity, in addition to distinctive titles and formulas, were introduced into many of the monographs. In that edition, specifications for basic drugs as well as dosage forms were included on a much larger scale than previously. Official formulas for a limited number of parenteral solutions under the class title "Ampuls" were published for the first time in the National Formulary. The fifth edition, published in 1926, did not differ materially from the preceding edition.

The Sixth and Seventh Editions of the National Formulary

In 1929, the Council of the American Pharmaceutical Association elected a new Committee on National Formulary. Under the capable direction of the Chairman of this Committee, Professor E. N. Gathercoal, a program was inaugurated and carried out which resulted in more far-reaching changes and greater progress in the technique of revising the National Formulary than in any previous period. A series of prescription surveys, published by the American Pharmaceutical Association in book form under the title, "The Prescription Ingredient Survey," was used as a basis for determining admissions to the sixth edition of the National Formulary, published in 1936. An unusually large number of obsolete drugs were discontinued, and numerous additional chemical, biological, and proximate assays were developed and introduced. One of the outstanding features of the sixth edition was the inclusion of monographs on a large number of ampuls and tablets with adequate standards of identity, strength, quality and purity, thus recognizing modern trends in dosage forms which previously had been neglected by the official compendia. The members of the Combined Contact Committee of the American Drug Manufacturers Association and the American Pharmaceutical Manufacturers' Association made outstanding contributions in the development of standards for ampuls and tablets.

By the time of the appearance of the sixth edition, it was evident that a new Federal Food, Drug, and Cosmetic Act, replacing the 1906 law, would be enacted. Plans in connection with the legislation indicated that a greatly strengthened and more comprehensive Act would place greater significance and importance upon official drug standards than obtained under the 1906 law. Accordingly, the Committee on National Formulary immediately began a study of the specifications in the new edition which were not entirely satisfactory.

Prior to 1936, the work incidental to the establishment of National Formulary standards was done voluntarily and gratuitously by the members of the Committee. The problems which evolved in connection with the sixth edition were so extensive that it was necessary to inaugurate a new and more efficient procedure whereby inadequate standards could be investigated and corrected more promptly than had been possible previously. Provision was made by the American Pharmaceutical Association in 1936 for the establishment of a well-equipped laboratory to serve as a clearing house for the research necessary in the establishment of adequate drug standards. This laboratory was installed in the Headquarters Building of the Association in 1938.

Other changes in policy relating to the National Formulary, adopted or inaugurated by the Council of the American Pharmaceutical Association after the publication of the sixth edition, included provision for the issuance of interim revision supplements, provision for issuance of the National Formulary at five-year instead of ten-year intervals, and a change in the organization of the Committee.

By means of Interim Revision Announcements, necessary corrections in the sixth edition monographs were issued as promptly as possible. The *Bulletin of the National Formulary Committee*, issued as a periodical upon a subscription basis, was used for the dissemination of all information concerning the National Formulary.

The decision to issue revisions of the National Formulary at five-year instead of ten-year intervals was necessary because of the rapid advancements and changes in the types of drugs employed. When the principle of more frequent revisions was adopted, the revision program was placed on a continuous basis, and activated by the provision for an Executive Committee of ten members with a chairman to serve as a full time employee of the American Pharmaceutical Association. The reorganization of the Committee on National Formulary also provided for designation of the chairman as *Director of Revision*. This small Executive Committee with power to act has made it possible to issue Interim Revision Announcements promptly, and has promoted the smooth functioning of a continuous program.

A Committee was elected under the new design of organization in 1939. When this Committee began to function early in 1940, it found that plans for the seventh edition had been well advanced by the previous Committee. The seventh edition, published in 1942, was for the most part an extension of the sixth edition, but with many new specifications added, and unsatisfactory standards corrected. The seventh edition also included a much enlarged and thoroughly revised section on materials and preparations for use in the clinical laboratory. In the process of revision, several sixth edition National Formulary monographs were transferred to the United States Pharmacopeia, and the majority of the USP XI monographs not admitted to USP XII were incorporated in the seventh edition of the National Formulary in order to provide for the continuance of official standards. In connection with the seventh edition it was necessary to issue five supplements. Their issuance provided mainly for replacements of drugs and pharmaceutical necessities employed in National Formulary preparations which became unavailable during World War II.

The Eighth and Ninth Editions of the National Formulary

Immediately after the publication of the seventh edition in May, 1942, work was started on its revision. Surveys of limited scope were conducted to aid the Committee in reaching decisions on deletions and new admissions for the eighth edition. When final decisions on these questions were made during the early part of 1944, it became apparent that again the National Formulary was to undergo a more extensive revision than at any time in the past. It was decided to discontinue official standards for a number of drugs, mostly of botanical origin, which had become obsolete. Monographs on several drugs were also discontinued because of their admission to USP XIII. Approval of the admission of approximately 100 new drugs was given by the Committee. The staff of the American Pharmaceutical Association Laboratory, assisting the members of the Committee and other collaborators, then developed tentative specifications which were published in the *Bulletin of the National Formulary Committee*. Since all specifications were based upon the results of extensive laboratory investigation, few adverse criticisms were received, this again illustrating the advantage of available laboratory facilities for any drug standardization project. In addition to admitting previously unofficial drugs, the Committee also voted to continue official recognition of a large number of pharmacopeial drugs not admitted to USP XIII.

The eighth edition of the National Formulary, the second published under the plan adopted in 1938 for more frequent revisions, was published in November, 1946. The provisions of the new standards became effective April 1, 1947, thus giving pharmacists time to familiarize themselves with the new edition, and pharmaceutical manufacturers an opportunity to make necessary changes in labels before compliance with the standards was compulsory.

Admissions of drugs to the eighth edition were based upon extent of use and therapeutic value. In addition to extensive changes in content of the National Formulary, numerous editorial changes were made, including the transposition of Latin and English titles, and the use of metric weights and measures was emphasized.

The ninth edition of the National Formulary was published in July, 1950, and became official November 1, of the same year. This edition included specifications for 717 drugs and dosage forms of which 155 had not been in the previous editions.

Essentially the same procedures as those employed in the revision of NF VIII were followed. Admissions to this edition were based, in part, on extent of use as determined by surveys designed to furnish the background information required, but therapeutic value was considered to a greater extent than in previous editions.

One Supplement to NF IX was issued in 1950, and one Interim Revision Announcement was published in 1952 for the correction of errors and the revision of a limited number of specifications.

The Tenth and Eleventh Editions of the National Formulary

The tenth edition of the National Formulary was published in August, 1955, and became official on December 15 of the same year. Two Interim Revision Announcements were issued, one of which became effective December 15, 1955, and the other on October 1, 1956.

During the revision of the ninth edition of the National Formulary, leading to the publication of the tenth, substantial changes in the content of the text were made. Of the 717 monographs in NF IX, 242 were not admitted to NF X. Titles and standards for 259 drugs, for which official standards would not otherwise have been provided were added to NF X during the revision period. In the process of revision, many individual specifications for strength, quality, purity, and identity were revised and materially improved.

In 1951 the *Bulletin of the National Formulary Committee* was re-titled *Drug Standards* and many of the new specifications were published therein for review and comment.

Several new features were added to NF X. Among these were specifications for the disintegration time of coated, buccal, and sublingual tablets; weight variation standards for the content of dry-filled capsules; and for solubility of hypodermic tablets. Through the efforts of a joint USP and NF Panel on Sterility Requirements, the general chapters on injections and sterility tests were revised and a new chapter on general sterilization procedures was prepared. A new section on general information was added to NF X. This section included specifications for prescription balances, weights and measuring devices; formulas for clinical laboratory reagents; a selected list of drugs and formulas for preparations used by chiropodists; basic information relating to dyes for use in coloring pharmaceutical preparations; a table comparing the names and standards of strength of drugs covered in the International Pharmacopoeia with those appearing in NF X; and a description of general sterilization procedures.

The section on clinical laboratory reagents and the table of optical crystallographic characteristics of NF medicinal chemicals underwent considerable revision and were transferred to the general information section.

The eleventh edition of the National Formulary—the last of five editions issued under the direction of Dr. J. L. Powers—was published in July, 1960, and became official October 1, 1960. Subsequently, four interim revision announcements were issued which became effective January 1, 1961; May 1, 1962; February 1, 1963; and May 1, 1963. As in the case of the preceding volume, NF XI was marked by a large number of new admissions, 285, which together with the 531 monographs admitted from NF X provided a total of 816 monographs. At the same time, 208 of the articles in the previous edition were no longer accorded NF recognition.

NF XI presented a marked change in typography and style, with use of a two-column format for the first time. In addition, the tests and assays reflected somewhat greater use of the new analytical techniques which were beginning to gain widespread acceptance for both quality control and enforcement purposes. This required a substantial increase in the number of reference standards, from ten in NF X to forty-two in NF XI.

The Twelfth Edition of the National Formulary

Probably the most distinguishing feature of the twelfth edition—particularly from an historical standpoint—was adoption of a sweeping new criterion for determining admission of drugs to the National Formulary. As heralded in the preface to that edition, the philosophy of *extent of use*, which had been the traditional criterion for recognition of articles in the NF, was struck down and eliminated. In its place, the concept of *therapeutic value* was established as the sole basis for inclusion of a drug in the compendium. This action served to elevate the importance of the compendium as a guide to rational medical practice, and raised the stature of the NF within the medically-related community. Not only did this action anticipate the action of Congress in the 1962 Drug Amendments, whereby effectiveness was introduced as a new requirement for the marketing of drugs, but presumably was influential in subsequently moving Congress to include the NF in the Medicare amendments to the Social Security law.

The great impact of instrumentation in pharmaceutical analysis for the first time was reflected in the individual NF monographs. Ultraviolet spectrophotometry had been employed to some extent in the eleventh edition, but it was in NF XII that instrumentation was fully accepted and embraced as a general approach to the establishment of drug standards and specifications.

However, with the general adoption of instrumentation, the need for suitable samples of reference substances to be used for comparative testing purposes also mushroomed. From a mere handful—ten in the case of NF X—the number of NF Reference Standards rose to almost one hundred. While still ancillary to the compendium itself, supplying this number of reference substances required a major expansion of this phase of the overall program to the point where in itself the Reference Standards activity became a significant facet of the total operation of establishing specifications.

The individual monographs, as presented in NF XII, were also affected in other ways as the result of the 1962 Drug Amendments. Previously, synonyms had been in wide use and were included by name in the pertinent monographs. This practice was specifically prohibited by the directive from Congress. Furthermore, batch certification—with the concomitant power for FDA to set specifications—was extended to all antibiotics. Taking this development into account, the NF deleted all standards and specifications from all the antibiotic monographs, in order to avoid any confusion which would result from dual and possibly even conflicting standards. Abbreviated monographs for antibiotics were still included in the NF to indicate their accepted therapeutic value as determined by the Committee on Admissions and to give related information of interest to pharmaceutical and medical practitioners.

Early during the revision period leading to NF XII, the American Medical Association and the United States Pharmacopeia joined with the American Pharmaceutical Association in sponsorship of the analytical laboratory facilities housed in the Association's building and operated under the auspices of the APhA Foundation. Through this mutual support and cooperation, the Drug Standards Laboratory was revitalized and by the close of the revision period was making a significant contribution to the NF program by providing direct, convenient laboratory services.

A thorough overhauling of all graphic formulas and all systematic chemical names was also instituted in NF XII to bring these into accord with the latest approved practices of recognized authoritative groups such as Chemical Abstracts Service and the International Union of Pure and Applied Chemistry (IUPAC). Furthermore, all molecular weights and assay calculation factors were recalculated on the basis of carbon-12 rather than oxygen-16, as previously employed. This change was in line with the 1961 revision of International Atomic Weights which changed the element of reference.

NF XII was published in early January 1965 and became official September 1, 1965. Subsequently, two supplements were issued which became effective on September 1, 1965, and on March 1, 1967, respectively. Issuance of supplements revived a practice which had not been utilized during the several previous revision periods. One interim revision announcement was also issued, which became official April 1, 1968. Continuing the trend of the last two editions, there were many new admissions to NF XII (248) to provide a total of 783 articles in the volume itself—another 19 articles were admitted by way of the supplements. At the same time, 280 monographs in NF XI were not voted admission to the new edition.

During the period covered by the thirteen editions of the National Formulary, many individuals have served as members of the revision bodies. Their names may be found by reference to previous editions of the National Formulary. The names of the Chairmen of the National Formulary Boards (or, as previously referred to, Committees on National Formulary), the years served by each, and the editions published during each corresponding period are tabulated below:

CHAIRMEN	NF EDITIONS	YEARS
Charles Rice	I	1883–1888
C. Lewis Diehl	II, III, IV	1889–1917
Wilbur L. Scoville	V	1919–1929
Edmund N. Gathercoal	VI	1930–1940
Justin L. Powers	VII, VIII, IX, X, XI	1940–1960
Edward G. Feldmann	XII, XIII	1960–1969

NATIONAL FORMULARY CODIFICATION*

Establishment and Organization of the National Formulary

Article I. Definition

The National Formulary, including Supplements and Interim Revision Announcements thereto, shall be a compendium of standards designed to ensure the safety, effectiveness, quality, and purity of drugs. Such standards shall include the titles, definitions, descriptions, and specifications (including test procedures and assays for the determination of the standards so established) appropriately developed and established to ensure adequate and appropriate characteristics of quality, strength, purity, and identity of the articles to which the respective standards apply.

Article II. Functions of the Board of Trustees

Pursuant to the provisions of Article II, A, 1 of the Constitution and Chapter III, Article II of the ASSOCIATION By-Laws, the Board of Trustees shall provide for the compilation and publication of the National Formulary, including Supplements and Interim Revision Announcements thereto. To this end, it shall do the following:

A. Provide for the publication and dissemination of successive editions of the National Formulary and for such Supplements and Interim Revision Announcements thereto as may be promulgated from time to time.

B. Receive and consider for approval the Statement of General Principles and other matters of significant general policy which the National Formulary Board may formulate concerning the program of maintaining and revising the National Formulary.

C. Receive and review periodic reports on the status and progress of the revision and publication program submitted to it by the Director of the National Formulary.

D. Receive and consider for budgetary approval proposed plans and contracts for the printing and distribution of each new edition of the National Formulary.

E. Review and consider for approval proof copies of each proposed revised edition of the National Formulary, or Supplement or Interim Revision Announcement thereto. When publication is authorized, the Board of Trustees shall approve the date on which the new edition of the National Formulary, or Supplement, or Interim Revision Announcement shall take effect and become official.

F. Establish the sale price for the National Formulary and for National Formulary Reference Standards.

G. Consider and approve the payment of any consultant fees or honoraria, when such a recommendation is made in connection with the National Formulary revision program.

H. Review all decisions of the National Formulary Board in accordance with the procedure established in these ASSOCIATION By-Laws.

Article III. The National Formulary Board

The National Formulary, including Supplements and Interim Revision Announcements thereto, shall be compiled under the direction of the National Formulary Board, elected by the Board of Trustees. Such Board shall consist of the Director of the National Formulary, a Secretary, and nine (9) elected members. Each member shall be elected to serve for a period of five (5) years or until a successor, having been duly elected, has assumed the duties of his office. The members elected shall be selected from a panel of experts who are generally recognized as being qualified to evaluate (in their respective fields) the safety, effectiveness, quality, and purity of drugs and to prescribe standards and specifications for drugs and other articles which may be used in connection with drugs. At least one (1) of the members of the Board shall be a physician and the other members shall be qualified in the pharmaceutical and related sciences. In selecting a candidate for election, due regard shall be had for his qualifications to serve as a member of the Board as evidenced by both his professional training and experience and by his professional standing and reputation in the area of the pharmaceutical and related sciences. In carrying out its functions, the Board shall do the following:

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* These articles of Codification of the National Formulary constitute Chapter XIV of the By-Laws of the American Pharmaceutical Association, as amended through 1969.

A. Meet at the call of the Director of the National Formulary, but in any event at least once a year. The presence of eight (8) members, including the Director and the Secretary, at any meeting of the Board shall constitute a quorum. The Board may take action at such a meeting by affirmative vote by a majority of the members present and voting. Matters pertaining to the Board's business requiring action between meetings may be submitted to the members of the Board by mail ballot accompanied by a suitably designed letter, circular, or bulletin, outlining the issues implicit in the question submitted for a vote.

B. At or near the beginning of each revision period, formulate a Statement of General Principles to be followed in the compilation of the National Formulary which shall serve as the general policy concerning planning and implementing the revision program of the National Formulary and the issuance of new editions, Supplements, and Interim Revision Announcements. Such general principles and policies shall be submitted to the Board of Trustees for approval, and, after approval, shall be made public.

C. Consider and act upon all proposals and recommendations made by the National Formulary committees and advisory panels, or from any other source, for revision of, additions to, and omissions from the National Formulary text.

D. Promulgate such revisions in the present official edition of the National Formulary as is deemed advisable or necessary to ensure a current compendium. In undertaking such revision, each member of the Board shall review and consider revising such portions of the current edition of the National Formulary, and the preparation of proposed new text for the National Formulary, as are assigned to him by the Director of the National Formulary. All revisions shall be consistent with the Statement of General Principles to be followed in the preparation of the next edition of the National Formulary. Upon completion of the assignment of each individual Board member, the entire Board shall review, and consider for approval, the final text of the manuscripts submitted by the individual members.

E. Recommend to the Board of Trustees the date on which the new edition of the National Formulary, or Supplement or Interim Revision Announcement thereto, shall take effect and become official.

F. Establish a Committee on Admissions and a Committee on Specifications, as hereinafter provided.

G. Consider and act upon proposals for admission to the National Formulary of any of those nontherapeutic substances used in the fabrication of dosage forms which are usually referred to as "pharmaceutical necessities" or "pharmaceutic aids."

H. Where deemed necessary, approve the establishment and preparation of authentic samples of various substances required for use as Reference Standards in National Formulary assays, tests, and for related purposes.

I. Through the Director of the National Formulary, recommend to the Board of Trustees the removal, for cause, of any member of the Committee on Admissions or of the Committee on Specifications.

J. Consider and act upon any other matter relating to the safety, effectiveness, quality, and purity of drugs and their safe use, when, in the judgment of the Board, such action is deemed desirable.

K. The National Formulary Board may promulgate such additional rules and regulations, and adopt such procedures, consistent with the Constitution and ASSOCIATION By-Laws, as it deems necessary to ensure the accuracy and adequacy of the National Formulary.

Article IV. Administrative Officers

The administrative officers of the National Formulary shall be a Director of the National Formulary, who shall be a full-time member of the ASSOCIATION staff, and a Secretary. Each shall be elected for a five (5) year term of office by a majority vote of the Board of Trustees and each shall hold office for the elected term and until such time when a successor, having been duly elected, has assumed the duties of his office. In the event of a vacancy in an office by resignation, death, or any incapacity to serve, the Chairman of the Board of Trustees may appoint a successor, *pro tempore*, who shall serve in such office until a successor shall have been elected and shall have assumed office. The Board of Trustees may remove any officer from office for cause.

Article V. Director of the National Formulary

The Director of the National Formulary shall be the chief administrative officer of the National Formulary Board. He shall have executive supervision over all of the activities of the Board, including direction of the activities of all committees, special panels, consultants, and other personnel, which may be established, retained, or employed from time to time to conduct the program and affairs of the National Formulary. He shall be an *ex officio* member, with vote, of the National Formulary Board, act as its Chairman, and preside at all of its meetings. He shall also be an *ex officio* member, without vote, of all committees and panels established in connection with any of the functions of the Board.

In carrying out his duties as the chief administrative officer of the National Formulary Board, the Director of the National Formulary shall, in addition to such functions as are implicit in his office as chief administrative officer, perform the following functions:

A. Establish, when deemed necessary or advisable, specific advisory panels, or engage consultants, to consider general or special subjects relating to the development of specifications for articles admitted to the National Formulary.

B. Coordinate all phases of the revision and publication program. His office shall operate as the administrative center for the various activities in the National Formulary program. He shall assign specific portions of any current National Formulary text to individual members of the National Formulary Board for detailed review and revision, when, in the opinion of such member, a need for revision is indicated.

C. Establish appropriate communications systems with the National Formulary Board, the Committee on Admissions, and the Committee on Specifications to ensure the systematic and orderly operation of these groups in their assigned responsibilities. He shall arrange for the compilation of all approved additions to, omissions from, or revisions in the National Formulary, and shall supervise the preparation of the final manuscript of the National Formulary.

D. Provide for the printing and wide distribution to members of pertinent scientific communities for review and comment of galley proof and page proof of new editions of the National Formulary, and shall arrange for an Open Conference at an appropriate time near the end of each revision period, to provide a forum for public comment on the proposed text of the new edition.

E. Arrange for the printing, distribution, and publicity of each new edition of the National Formulary, or Supplement or Interim Revision Announcement thereto, and present appropriate plans to the Board of Trustees for its consideration and budgetary approval.

F. Whenever a revised edition of the National Formulary, or Supplement or Interim Revision Announcement thereto, has been completed and approved by the National Formulary Board, inform the Board of Trustees and transmit sufficient proof copies of the proposed publication to the Board of Trustees for its review, consideration, and approval for publication as provided in the ASSOCIATION By-Laws.

G. Provide for the standardization, packaging, labeling, and distribution of authentic samples of various substances deemed necessary by the National Formulary Board as Reference Standards in National Formulary assays, tests, and for related purposes.

H. Submit written reports to the Board of Trustees, at least annually, reporting on the progress and affairs of the revision and publication program.

I. Call the meetings of the National Formulary Board, prepare a detailed agenda for each meeting, and preside at all meetings.

J. Nominate candidates for election as members of the Committee on Admissions and of the Committee on Specifications at the beginning of each new revision period. After approval of the candidates by the National Formulary Board, he shall submit the nominations to the Board of Trustees for consideration and election to office. The list of candidates for election to membership on the Committee on Admissions shall include at least twenty (20) nominations and the list for election to membership on the Committee on Specifications at least fifty (50) nominations.

K. Nominate candidates for filling vacancies which may occur on the National Formulary Board, the Committee on Admissions, or the Committee on Specifications, and after approval by the National Formulary Board, submit his list of candidates to the Board of Trustees for consideration and election.

L. Upon what seems to him sufficient cause, recommend to the Board of Trustees removal of any member of the National Formulary Board, the Committee on Admissions, or the Committee on Specifications.

Article VI. Secretary

The Secretary shall keep fair and sufficiently complete summary minutes of meetings of the National Formulary Board, committees, and advisory panels to reflect the proceedings of such meetings accurately; preserve all reports and communications received by the National Formulary Board; and perform such other duties pertaining to the management of the affairs of the National Formulary Board as may be assigned to him by the Director of the National Formulary.

Article VII. Committee on Admissions

The Committee on Admissions of the National Formulary shall consist of the physician member of the National Formulary Board, who shall act as the Chairman of the Committee, and nineteen (19) additional members, sixteen (16) of whom shall be physicians or pharmacologists. The members of the Committee shall be elected by the Board of Trustees from a list of candidates nominated by the Director of the National Formulary and approved by the National Formulary Board. Each member shall be elected to serve for a term of five (5) years. Any member may be removed by the Board of Trustees for cause.

The Committee on Admissions shall perform the following functions:

A. Consider and act upon appropriate matters submitted to it by the Director of the National Formulary for consideration and action. Except as may be otherwise provided in the ASSOCIATION By-Laws, the Committee's action shall be consistent with basic policy established by the National Formulary Board from time to time. All Committee decisions shall be transmitted to the National Formulary Board by the Director of the National Formulary for consideration and action.

B. In considering eligibility of an article for admission to the National Formulary, determine the therapeutic value of the article proposed for admission and select for admission only articles considered by it to possess demonstrated therapeutic value and usefulness. Suitable dosage forms for the administration of such articles may be determined for admission by a special subcommittee of five (5) members, appointed by the Director of the National Formulary, primarily from the membership of the Committee itself. The Committee may, at its discretion, approve for admission specific dosage forms containing rational combinations of official drugs. Approval of an article for recommendation for admission to the National Formulary shall be by an affirmative vote of not less than two-thirds ($^2/_3$) of the ballots cast by the members of the Committee voting, providing that not less than fifteen (15) votes are cast; and provided, further, that approval of a dosage form for recommendation for admission by the subcommittee shall be by an affirmative vote of not less than three (3) members of the subcommittee.

C. Review and consider for approval recommendations for admission of therapeutic substances and dosage forms submitted by duly constituted National Formulary advisory panels of experts in paramedical specialty fields. Approval of an article or dosage form thus recommended shall be an affirmative vote of a simple majority of the ballots cast by the Committee on Admissions, provided not less than fifteen (15) votes are cast.

D. Review and consider for approval the pharmacological category statements and the dose statements proposed for inclusion in the National Formulary monographs for therapeutic articles. When requested by the Director of the National Formulary, members of the Committee on Admissions, either individually or as a panel designated by the Director of the National Formulary, shall recommend, for inclusion in the National Formulary, caution statements and related information of a medical nature pertaining to the effective and safe use of drugs.

Article VIII. Committee on Specifications

The Committee on Specifications shall consist of fifty (50) members, broadly representative of the pharmaceutical, chemical, and biological sciences. The members of the Committee shall be elected by the Board of Trustees from a list of candidates nominated by the Director of the National Formulary and approved by the National Formulary Board. Each member shall be elected to serve for a term of five (5) years. Any member may be removed by the Board of Trustees for cause.

The Committee on Specifications shall function in an advisory capacity, in developing standards, specifications, test procedures, and assays, as may be required, for articles recommended for admission to the National Formulary. Where appropriate, the Director of the National Formulary shall transmit recommendations ensuing from the Committee to the National Formulary Board for its information or approval.

The members of the Committee on Specifications, either individually or as panels designated by the Director of the National Formulary, shall assist in the development of tests, specifications, and other standards for articles which have been approved for admission to the National Formulary.

When requested by the Director of the National Formulary, members of the Committee, either as individuals or as panels designated by the Director of the National Formulary, shall serve in an advisory capacity on any other matter of a specifications nature which may be submitted for consideration by the Director of the National Formulary.

Article IX. General

A. Members of the National Formulary Board, committees, and panels shall adhere to principles enunciated in the National Formulary Board's Statement of Philosophy of Conduct in carrying out their respective assignments.

B. Except where otherwise provided in the ASSOCIATION By-Laws, all actions by the National Formulary Board, its committees and panels, shall be taken by majority vote of the members present at a meeting, provided a quorum is present; or by a majority mail vote, provided the mail votes cast equal in number the quorum required of that body voting at a meeting.

C. Any vacancy on the National Formulary Board, the Committee on Admissions, or the Committee on Specifications, which may occur during the interim period, shall be filled by election by the Board of Trustees of a successor member to fill such vacancy for the unexpired term.

D. 1. Proposals for admission of drugs, and the inclusion of pertinent category and dosage statements in the National Formulary, and proposals for deletion of drugs or the revision of any category and dosage statements in the National Formulary, emanating from the Committee on Admissions, shall be made to the National Formulary Board for consideration and action through the Director of the National Formulary.

2. Suggested standards and specifications, including appropriate tests and assays, for articles which have been qualified for admission to the National Formulary, or suggested revisions of such specifications, tests, and assays for articles appearing in the National Formulary, emanating from members or panels of the Committee on Specifications, or from other appropriate sources, shall be submitted to the National Formulary Board for consideration and action through the Director of the National Formulary.

3. The Director of the National Formulary shall review all proposals made by the Committee on Admissions and all suggested specifications, tests, and assays, as prepared by members or panels of the Committee on Specifications. If, after review, he deems it advisable that any proposal or suggested specification, test, or assay be remanded to the respective committee for further consideration, he may so remand it with his statement as to the reasons for the remand. In case of such remand, the committee shall review the prior recommendation in light of the statement of reasons for the remand, and may then either revise the recommendations or elect to return them to the Director of the National Formulary without revision. In the event of a return without revision, or upon approval of any committee's submittal by the Director of the National Formulary, he shall assign it to a member of the National Formulary Board of his selection for initial review and recommendation. A review of such submittal by such member shall be in accordance with the Statement of General Principles adopted by the National Formulary Board for the preparation of the next edition of the National Formulary. Upon conclusion of his review, the member shall transmit the proposal, with his recommendations, to the Director of the National Formulary for submission to the entire Board.

E. Upon review and consideration of any proposal submitted to it by the Committee on Admissions, the National Formulary Board may approve or disapprove the proposal.

F. Upon review and consideration of suggested standards and specifications, including tests and assays, submitted to it by members or panels of the Committee on Specifications, the National Formulary Board may:

1. Approve the submission;
2. Revise the submission and adopt it as so revised;
3. Remand the submission to the member of the Board having previously reviewed it for further consideration in light of guidelines for revision as established by the Board; such member may then undertake such revision on his own initiative or may remand it to the pertinent panel or members of the Committee on Specifications for revision; or
4. Reject the submission in its entirety.

G. When a decision to admit an article has been acted upon favorably by the National Formulary Board, that article shall be regarded, and announced, as being *provisionally* admitted;

When the monograph for a provisionally admitted article has been prepared in proof form and so publicized through distribution, the article shall be regarded and announced as being *tentatively* admitted; and

When the monograph for a tentatively admitted article has been included in the National Formulary, the article shall be regarded and announced as being *finally* admitted.

Article X. Appeals

The decision of the National Formulary Board with respect to any submittal received by it as provided in the ASSOCIATION By-Laws shall be final unless appealed to the Board of Trustees. Such appeals may be taken by the Director of the National Formulary on his own initiative; and such appeals shall be taken by him on request of any interested party. An appeal shall be perfected by transmitting a copy of the decision appealed from, accompanied by a memorandum summarizing the issue implicit in the appeal, to the Board of Trustees within sixty days of the announcement or publication of the decision. Appeals by interested parties shall be submitted to the Director of the National Formulary for transmittal to the Board of Trustees. The Board of Trustees shall consider and act upon all appeals as promptly as practicable. It may approve the decision by the National Formulary Board or, failing to approve, remand it for further review and consideration by that Board with an accompanying memorandum outlining the reasons for the remand. In the event of approval, the decision appealed from shall become final as of the date of such approval by the Board of Trustees. In the event of remand, the National Formulary Board shall review and take action on any remand by the Board of Trustees. It may then either reaffirm its original decision or revise it in whatever manner is deemed advisable in light of the recommendations made by the Board of Trustees. Either action by the National Formulary Board on such remands shall be final. All final decisions of admission, deletion, or revision shall be put into effect by following normal procedures in revising the National Formulary.

The following is excerpted from the Constitution of the American Pharmaceutical Association; as amended through 1969:

Article II. Objects. This ASSOCIATION shall exist for the following purposes:

A. To aid in improving, promoting, and safeguarding the public health and welfare in every practical manner and by all practical means—

(1) By maintaining a compendium of standards and specifications calculated to promote the safety, efficacy, and purity of drugs, to be known as "The National Formulary." Criteria for establishing such standards and specifications, and the procedures to be followed in qualifying an article for admission to The National Formulary, shall be established by a Board, elected by the Board of Trustees, to be known as the "National Formulary Board"; and

(2) By promoting the safe use of drugs and aiding in the detection and prevention of adulteration and misbranding of drugs and medicines, and by taking such steps, as an ASSOCIATION and in cooperation with other organizations, as will assure the production and distribution of drugs and medicines of the highest quality, in a manner consistent with practices deemed reasonably necessary to ensure their purity and safety.

New Admissions to NF XIII

A

Acetaminophen Elixir
Acetohexamide
Acetohexamide Tablets
Acetophenazine Maleate
Acetophenazine Maleate Tablets
Acetyldigitoxin
Acetyldigitoxin Tablets
Aluminum Aspirin Tablets
Alverine Citrate
Alverine Citrate Tablets
Amantadine Hydrochloride
Amantadine Hydrochloride Capsules
Amantadine Hydrochloride Syrup
Ambenonium Chloride
Ambenonium Chloride Tablets
Aminoacetic Acid Sterile Solution
Aminocaproic Acid
Aminocaproic Acid Injection
Aminocaproic Acid Tablets
Angiotensin Amide
Angiotensin Amide for Injection
Anisindione
Anisindione Tablets
Antipyrine and Benzocaine Solution
Aprobarbital Elixir
Ascorbyl Palmitate

B

Bendroflumethiazide
Bendroflumethiazide Tablets
Benzonatate
Benzonatate Capsules
Benzphetamine Hydrochloride
Benzphetamine Hydrochloride Tablets
Benzthiazide
Benzthiazide Tablets
Benzyl Benzoate Lotion
Betamethasone Cream
Betamethasone Acetate
Betamethasone Sodium Phosphate
Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension, Sterile
Betamethasone Valerate
Betamethasone Valerate Cream
Biperiden
Biperiden Hydrochloride
Biperiden Hydrochloride Tablets
Biperiden Lactate Injection
Bisacodyl
Bisacodyl Suppositories
Bisacodyl Tablets
Boric Acid
Bromodiphenhydramine Hydrochloride
Bromodiphenhydramine Hydrochloride Capsules
Bromodiphenhydramine Hydrochloride Elixir
Butalbital

C

Calcium Aminosalicylate Capsules
Calcium Benzoylpas
Calcium Benzoylpas Tablets
Calcium Ipodate
Calcium Ipodate for Oral Suspension
Calcium Oxytetracycline
Calcium Oxytetracycline Oral Suspension
Calcium Phosphate, Dibasic
Candicidin
Candicidin Ointment
Candicidin Suppositories
Carbarsone
Carbarsone Tablets
Carbinoxamine Maleate Elixir
Carphenazine Maleate
Carphenazine Maleate Tablets
Chloral Betaine
Chloral Betaine Tablets
Chlorcyclizine Hydrochloride
Chlorcyclizine Hydrochloride Tablets
Chlordiazepoxide
Chlordiazepoxide Tablets
Chlormadinone Acetate
Chlormadinone Acetate and Mestranol Tablets
Chloroprocaine Hydrochloride
Chloroprocaine Hydrochloride Injection
Chlorothiazide Oral Suspension
Chlorprothixene
Chlorprothixene Tablets
Chymotrypsin, Sterile
Chymotrypsin Injection
Clidinium Bromide
Clofibrate
Clofibrate Capsules
Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets
Colistin Sulfate
Colistin Sulfate for Oral Suspension
Cyanocobalamin Co 60 Capsules
Cyanocobalamin Co 60 Solution
Cyclothiazide
Cyclothiazide Tablets
Cyproheptadine Hydrochloride
Cyproheptadine Hydrochloride Syrup
Cyproheptadine Hydrochloride Tablets

D

Danthron Tablets
Demeclocycline
Demeclocycline Hydrochloride Tablets
Desipramine Hydrochloride
Desipramine Hydrochloride Capsules
Desipramine Hydrochloride Tablets
Dexamethasone Aerosol
Dexbrompheniramine Maleate
Dexbrompheniramine Maleate Tablets
Dextriferron Injection
Diazepam
Diazepam Injection
Diazepam Tablets
Dibucaine Cream
Dibucaine Ointment
Dichlorodifluoromethane

Dichlorotetrafluoroethane
Dicyclomine Hydrochloride
Dicyclomine Hydrochloride Capsules
Dicyclomine Hydrochloride Syrup
Dienestrol Cream
Diethylpropion Hydrochloride
Diethylpropion Hydrochloride Tablets
Dihydroxyaluminum Sodium Carbonate
Dihydroxyaluminum Sodium Carbonate Tablets
Dimethindene Maleate
Dimethindene Maleate Syrup
Dimethindene Maleate Tablets
Dimethisterone
Dioctyl Calcium Sulfosuccinate
Dioctyl Calcium Sulfosuccinate Capsules
Dioctyl Sodium Sulfosuccinate Solution
Dioctyl Sodium Sulfosuccinate Syrup
Diphenoxylate Hydrochloride
Diphenoxylate Hydrochloride and Atropine Sulfate Solution
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets
Doxapram Hydrochloride
Doxapram Hydrochloride Injection
Dromostanolone Propionate
Dromostanolone Propionate Injection
Dydrogesterone
Dydrogesterone Tablets

E

Ergotamine Tartrate and Caffeine Suppositories
Ergotamine Tartrate and Caffeine Tablets
Erythrityl Tetranitrate, Diluted
Erythrityl Tetranitrate Tablets
Erythromycin Ethylsuccinate
Erythromycin Ethylsuccinate Injection
Erythromycin Ethylsuccinate for Oral Suspension
Erythromycin Ethylsuccinate Tablets
Ethamivan
Ethamivan Injection
Ethinyl Estradiol and Dimethisterone Tablets
Ethyl Chloride

F

Fluocinolone Acetonide
Fluorometholone
Fluorometholone Cream
Fluphenazine Enanthate
Fluphenazine Enanthate Injection
Fluphenazine Hydrochloride
Fluphenazine Hydrochloride Injection
Fluphenazine Hydrochloride Tablets
Fluprednisolone
Fluprednisolone Tablets
Flurandrenolide
Flurandrenolide Cream
Flurandrenolide Ointment
Flurothyl
Fluroxene

G

Gitalin
Gitalin Tablets
Glyceryl Guaiacolate
Glyceryl Guaiacolate Syrup
Glycopyrrolate
Glycopyrrolate Tablets

H

Haloperidol
Haloperidol Solution
Haloperidol Tablets
Hydrocortisone Lotion
Hydroflumethiazide
Hydroflumethiazide Tablets
Hydroquinone
Hydroquinone Ointment
Hydroxyzine Hydrochloride Injection
Hydroxyzine Hydrochloride Syrup
Hydroxyzine Pamoate
Hydroxyzine Pamoate Capsules
Hydroxyzine Pamoate Oral Suspension
Hyoscyamine Sulfate Tablets

I

Indomethacin
Indomethacin Capsules
Iodochlorhydroxyquin and Hydrocortisone Cream
Iodochlorhydroxyquin and Hydrocortisone Lotion
Iodochlorhydroxyquin and Hydrocortisone Ointment
Isocarboxazid
Isocarboxazid Tablets
Isopropamide Iodide
Isopropamide Iodide Tablets
Isoproterenol Sulfate Aerosol
Isoxsuprine Hydrochloride
Isoxsuprine Hydrochloride Tablets

L

Levopropoxyphene Napsylate
Levopropoxyphene Napsylate Capsules

M

Magaldrate
Magaldrate Oral Suspension
Magaldrate Tablets
Menadione
Menadione Tablets
Mepenzolate Bromide
Mepenzolate Bromide Tablets
Meperidine Hydrochloride Syrup
Meprobamate Oral Suspension
Mestranol Tablets
Methacycline Hydrochloride
Methacycline Hydrochloride Capsules
Methacycline Hydrochloride Oral Suspension
Methandrostenolone
Methandrostenolone Tablets
Methapyrilene Hydrochloride Capsules
Methdilazine
Methdilazine Tablets
Methdilazine Hydrochloride

Methdilazine Hydrochloride Syrup
Methdilazine Hydrochloride Tablets
Methocarbamol
Methocarbamol Injection
Methocarbamol Tablets
Methotrimeprazine
Methotrimeprazine Injection
Methoxyflurane
Methyclothiazide
Methyclothiazide Tablets
Methylbenzethonium Chloride Powder
Methyprylon Capsules
Methysergide Maleate
Methysergide Maleate Tablets

N

Nalidixic Acid
Nalidixic Acid Tablets
Nandrolone Decanoate
Nandrolone Decanoate Injection
Nandrolone Phenpropionate
Nandrolone Phenpropionate Injection
Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream
Neomycin Sulfate and Hydrocortisone Acetate Lotion
Neomycin Sulfate, Polymyxin B Sulfate, and Gramicidin Ophthalmic Solution
Neomycin Sulfate, Polymyxin B Sulfate, and Zinc Bacitracin Ointment
Nialamide
Nialamide Tablets
Nitrofurazone Cream
Norethandrolone
Norethandrolone Tablets
Norethindrone Acetate
Norethindrone Acetate Tablets
Norethindrone Tablets
Nortriptyline Hydrochloride
Nortriptyline Hydrochloride Capsules
Noscapine

O

Orphenadrine Citrate
Oxandrolone
Oxandrolone Tablets
Oxazepam
Oxazepam Capsules
Oxtriphylline
Oxtriphylline Tablets
Oxymetazoline Hydrochloride
Oxymetazoline Hydrochloride Solution
Oxymetholone
Oxymetholone Tablets
Oxymorphone Hydrochloride
Oxymorphone Hydrochloride Injection
Oxymorphone Hydrochloride Tablets
Oxyphenbutazone
Oxyphenbutazone Tablets
Oxyphencyclimine Hydrochloride
Oxyphencyclimine Hydrochloride Tablets
Oxytetracycline Injection

P

Paramethasone Acetate
Paramethasone Acetate Tablets
Pargyline Hydrochloride
Pargyline Hydrochloride Tablets
Paromomycin Sulfate
Paromomycin Sulfate Capsules
Pentaerythritol Tetranitrate, Diluted
Pentaerythritol Tetranitrate Tablets
Pentazocine
Pentazocine Lactate Injection
Peppermint Water
Perphenazine
Perphenazine Injection
Perphenazine Tablets
Phenazopyridine Hydrochloride
Phenazopyridine Hydrochloride Tablets
Phenprocoumon
Phenprocoumon Tablets
Phenylmercuric Acetate
Phenylpropanolamine Hydrochloride
Phthalylsulfathiazole
Phthalylsulfathiazole Tablets
Piminodine Esylate
Piminodine Esylate Injection
Piminodine Esylate Tablets
Pipobroman
Pipobroman Tablets
Polycarbophil
Polythiazide
Polythiazide Tablets
Posterior Pituitary
Posterior Pituitary Injection
Potash, Sulfurated
Potassium Gluconate
Potassium Gluconate Elixir
Potassium Gluconate Tablets
Potassium Phosphate, Monobasic
Potassium Sorbate
Povidone
Povidone-Iodine Aerosol
Prednisolone Succinate
Prednisolone Sodium Succinate for Injection
Prilocaine Hydrochloride
Prilocaine Hydrochloride Injection
Procaine Hydrochloride and Levonordefrin Injection
Procaine and Phenylephrine Hydrochlorides Injection
Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection
Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection
Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection
Procaine, Tetracaine, and Phenylephrine Hydrochlorides Injection
Propiomazine Hydrochloride
Propiomazine Hydrochloride Injection
Propoxyphene Hydrochloride and Aspirin Capsules
Pseudoephedrine Hydrochloride
Pseudoephedrine Hydrochloride Syrup
Pseudoephedrine Hydrochloride Tablets
Pyrrocaine Hydrochloride
Pyrrocaine Hydrochloride and Epinephrine Injection

R

Rolitetracycline
Rolitetracycline for Injection

S

Salicylamide Oral Suspension
Selenium Sulfide
Selenium Sulfide Detergent Suspension
Silicon Dioxide, Colloidal
Sodium Chlorothiazide for Injection
Sodium Citrate Solution, Anticoagulant
Sodium Dextrothyroxine
Sodium Dextrothyroxine Tablets
Sodium Ipodate
Sodium Ipodate Capsules
Sodium Novobiocin for Injection
Sodium Penicillin G for Injection
Sodium Secobarbital and Sodium Amobarbital Capsules
Sorbic Acid
Stanozolol
Stanozolol Tablets
Sulfaethidole
Sulfamethoxazole
Sulfamethoxazole Oral Suspension
Sulfamethoxazole Tablets
Sulfisoxazole and Phenazopyridine Hydrochloride Tablets

T

Tetracaine
Tetracaine Ophthalmic Ointment
Tetracycline Phosphate Complex
Tetracycline Phosphate Complex Capsules
Tetrahydrozoline Hydrochloride Ophthalmic Solution
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets
Thiethylperazine Maleate
Thiethylperazine Maleate Tablets
Thihexinol Methylbromide
Thimerosal Aerosol
Thioguanine
Thioguanine Tablets
Thiopropazate Hydrochloride
Thiopropazate Hydrochloride Tablets
Tranylcypromine Sulfate
Tranylcypromine Sulfate Tablets
Triacetin
Triacetin Aerosol
Triacetin Cream
Triacetin Powder
Triamcinolone Acetonide Aerosol
Triamcinolone Diacetate
Triamcinolone Diacetate Suspension, Sterile
Triamcinolone Diacetate Syrup
Trichlormethiazide
Trichlormethiazide Tablets
Trichloromonofluoromethane
Triclobisonium Chloride
Triclobisonium Chloride Cream
Triclobisonium Chloride Ointment
Triethylenemelamine Tablets
Trifluoperazine Hydrochloride
Trifluoperazine Hydrochloride Injection
Trifluoperazine Hydrochloride Tablets
Triflupromazine Hydrochloride
Triflupromazine Hydrochloride Tablets
Trimeprazine Tartrate
Trimeprazine Tartrate Syrup
Trimeprazine Tartrate Tablets
Trimethidinium Methosulfate
Trimethidinium Methosulfate Tablets
Trioxsalen
Trioxsalen Tablets
Triprolidine Hydrochloride
Triprolidine Hydrochloride Tablets
Troleandomycin Oral Suspension
Tromethamine
Tromethamine for Injection
Tuaminoheptane Sulfate Solution
Tybamate
Tybamate Capsules

V

Valethamate Bromide
Valethamate Bromide Injection
Vitamin E

W

White Lotion

X

Xylometazoline Hydrochloride
Xylometazoline Hydrochloride Solution

Articles Included in NF XII But Not Admitted to NF XIII

A

Acacia Mucilage
Adrenal Cortex Injection
Alum, Dried
Aluminum Hydroxide Gel, Dried
Aluminum Hydroxide Gel Dried, Tablets
Aminobenzoic Acid
Aminobenzoic Acid Tablets
Ammonium Bromide
Amphetamine Phosphate
Amphetamine Phosphate Injection
Amphetamine Phosphate Tablets
Antiseptic Solution, NF
Areca
Arecoline Hydrobromide
Arecoline Hydrobromide Tablets
Aromatic Elixir, Red
Aspirin, Phenacetin and Caffeine Capsules
Azacyclonol Hydrochloride
Azacyclonol Hydrochloride Tablets

B

Benzpyrinium Bromide
Benzpyrinium Bromide Injection
Benztropine Mesylate
Benztropine Mesylate Tablets
Bismuth Subnitrate Tablets
Bithionol
Boric Acid Solution
Bromides Elixir, Three
Bromides Tablets, Three
Brown Mixture
Butyl Chloride

C

Calamine Ointment
Calcium Chloride Injection
Calcium Cyclobarbital
Calcium Cyclobarbital Tablets
Calcium Gluconate Injection
Calomel
Calomel Tablets
Camphor Liniment
Camphor and Soap Liniment
Carbarsone Suppositories
Cardamom Oil
Cardamom Spirit, Compound
Chlordiazepoxide Hydrochloride
Chlordiazepoxide Hydrochloride Capsules
Chlordiazepoxide Hydrochloride for Injection
Chloroform Liniment
Chlorothymol
Choline Dihydrogen Citrate
Choline Dihydrogen Citrate Capsules
Choline Dihydrogen Citrate Tablets
Cinnamon Water
Cochineal
Cortisone Acetate
Cortisone Acetate Ophthalmic Suspension
Cortisone Acetate Suspension, Sterile
Cortisone Acetate Tablets
Creosote
Cyclophosphamide
Cyclophosphamide Tablets

D

Deslanoside
Deslanoside Injection
Dexamethasone
Dexamethasone Tablets
Dexamethasone Sodium Phosphate
Dextromethorphan Hydrobromide Tablets
Dibucaine Ophthalmic Ointment
Diethylstilbestrol Dipropionate Injection
Digitalis Tincture
Dioctyl Sodium Sulfosuccinate
Diphenylhydantoin
Doxylamine Succinate
Doxylamine Succinate Tablets
Drocarbil

E

Ephedrine Hydrochloride Capsules
Ephedrine Hydrochloride Tablets
Ephedrine Sulfate Injection
Ephedrine Sulfate Jelly
Ephedrine Sulfate Syrup
Epinephrine Bitartrate Ophthalmic Ointment
Ethyl Oxide
Eucalyptol

G

Gallamine Triethiodide
Gallamine Triethiodide Injection
Ginger
Ginger Oleoresin
Globin Zinc Insulin Injection
Glycyrrhiza Elixir
Glycyrrhiza Extract
Gold Au 198 Solution
Gold Sodium Thiosulfate
Gold Sodium Thiosulfate, Sterile

H

Halazone
Halazone Tablets
Honey
Hydriodic Acid, Diluted
Hydriodic Acid Syrup
Hydrocodone Bitartrate
Hydrocodone Bitartrate Syrup
Hydrocodone Bitartrate Tablets

I

Imipramine Hydrochloride
Imipramine Hydrochloride Injection
Imipramine Hydrochloride Tablets
Inositol
Iodoalphionic Acid
Iodoalphionic Acid Tablets

Isoflurophate Ophthalmic Solution
Isoproterenol Sulfate
Isoproterenol Sulfate Inhalation

L

Levallorphan Tartrate
Levallorphan Tartrate Injection
Lime
Lime Solution, Sulfurated
Liver Injection

M

Mannitol
Mannitol Injection
Menadione Capsules
Meperidine Hydrochloride
Meperidine Hydrochloride Injection
Meperidine Hydrochloride Tablets
Mephenesin
Mephenesin Capsules
Mephenesin Tablets
Mephentermine Sulfate
Mephentermine Sulfate Injection
Meprobamate
Meprobamate Tablets
Merbromin
Merbromin Solution
Merbromin Solution, Surgical
Mercurophylline
Mercurophylline Injection
Mercurophylline Tablets
Mercury Bichloride
Mercury Bichloride Large Poison Tablets
Metabutoxycaine Hydrochloride
Metabutoxycaine Hydrochloride and Epinephrine Injection
Methylphenidate Hydrochloride
Methylphenidate Hydrochloride for Injection
Methylphenidate Hydrochloride Tablets
Methylthiouracil Tablets
Methyprylon Elixir
Milk of Magnesia Tablets
Mouthwash, NF

N

Nordefrin Hydrochloride
Noscapine Hydrochloride

O

Oleandomycin Phosphate Capsules
Oxytetracycline
Oxytetracycline for Oral Suspension
Oxytetracycline Hydrochloride
Oxytetracycline Hydrochloride Capsules
Oxytetracycline Hydrochloride for Injection

P

Pepsin
Pepsin Elixir, Lactated
Phenindamine Tartrate Syrup
Pheniramine Maleate
Pheniramine Maleate Tablets
Phenothiazine
Phenoxymethyl Penicillin
Phenoxymethyl Penicillin Capsules
Phenoxymethyl Penicillin for Oral Suspension
Phenoxymethyl Penicillin Tablets
Phenylbutazone
Phenylbutazone Tablets
Pine Oil
Pine Tar Ointment
Pipradrol Hydrochloride
Pipradrol Hydrochloride Tablets
Potassium Bitartrate
Potassium Bromide
Potassium Phosphate
Pramoxine Hydrochloride Solution
Procaine Penicillin in Oil Injection
Procaine, Tetracaine, and Nordefrin Hydrochlorides Injection

Q

Quinidine Sulfate Capsules
Quinine Sulfate
Quinine Sulfate Capsules
Quinine Sulfate Tablets

R

Racephedrine Hydrochloride
Racephedrine Hydrochloride Capsules
Racephedrine Hydrochloride Solution
Rosemary Oil

S

Scopolamine Hydrobromide Tablets
Seidlitz Powders
Silver Nitrate Solution, Ammoniacal
Sodium Bromide
Sodium Bromide Elixir
Sodium Hexobarbital
Sodium Hexobarbital, Sterile
Sodium Iodomethamate
Sodium Iodomethamate Injection
Sodium Pentobarbital Tablets
Sodium Perborate
Sodium Perborate, Aromatic, NF
Sodium Phenobarbital Tablets
Sodium Sulfabromomethazine
Sodium Sulfamerazine Injection
Sodium Sulfate

T

Tannic Acid
Tannic Acid Glycerite
Testosterone Enanthate
Testosterone Enanthate Injection
Thenyldiamine Hydrochloride
Thenyldiamine Hydrochloride Tablets
Theobromine
Theophylline
Thiabendazole
Thimerosal Ointment
Thonzylamine Hydrochloride
Thonzylamine Hydrochloride Tablets
Thyme Oil
Thymol
dl-Alpha Tocopherol
d-Alpha Tocopheryl Acetate
dl-Alpha Tocopheryl Acetate
d-Alpha Tocopheryl Acetate Concentrate
d-Alpha Tocopheryl Acid Succinate
Tocopherols Concentrate, Mixed
Tragacanth Mucilage
Tyrothricin Solution
Tyrothricin Spray
Tyrothricin Troches

Complete List of Finally Admitted NF XIII Articles

A

Acacia Syrup
Acetaminophen
Acetaminophen Elixir
Acetaminophen Tablets
Acetic Acid, Diluted
Acetohexamide
Acetohexamide Tablets
Acetone
Acetophenazine Maleate
Acetophenazine Maleate Tablets
Acetyldigitoxin
Acetyldigitoxin Tablets
Acetyl Sulfisoxazole
Acetyl Sulfisoxazole Oral Suspension
Alcohol, Rubbing
Almond Oil
Alphaprodine Hydrochloride
Alphaprodine Hydrochloride Injection
Alum
Aluminum Aspirin
Aluminum Aspirin Tablets
Aluminum Chloride
Aluminum Phosphate Gel
Alverine Citrate
Alverine Citrate Tablets
Amantadine Hydrochloride
Amantadine Hydrochloride Capsules
Amantadine Hydrochloride Syrup
Amaranth Solution, Compound
Ambenonium Chloride
Ambenonium Chloride Tablets
Aminoacetic Acid
Aminoacetic Acid Sterile Solution
Aminocaproic Acid
Aminocaproic Acid Injection
Aminocaproic Acid Tablets
Ammonia Solution, Strong
Ammonia Spirit, Aromatic
Ammonium Carbonate
Amobarbital Elixir
Amodiaquine Hydrochloride
Amodiaquine Hydrochloride Tablets
Amphetamine Sulfate
Amphetamine Sulfate Injection
Amphetamine Sulfate Tablets
Amylene Hydrate
Amyl Nitrite
Angiotensin Amide
Angiotensin Amide for Injection
Anileridine
Anileridine Injection
Anileridine Hydrochloride
Anileridine Hydrochloride Tablets
Anisindione
Anisindione Tablets
Antazoline Phosphate
Antazoline Phosphate Ophthalmic Solution
Anthralin
Anthralin Ointment
Antipyrine
Antipyrine and Benzocaine Solution
Apomorphine Hydrochloride
Apomorphine Hydrochloride Tablets
Aprobarbital
Aprobarbital Elixir
Ascorbyl Palmitate
Aspirin Capsules
Aspirin, Phenacetin and Caffeine Tablets
Atropine
Azuresin

B

Belladonna Extract
Belladonna Leaf Fluidextract
Bendroflumethiazide
Bendroflumethiazide Tablets
Benzaldehyde
Benzaldehyde Elixir, Compound
Benzestrol
Benzestrol Tablets
Benzethonium Chloride
Benzethonium Chloride Solution
Benzocaine
Benzocaine Ointment
Benzonatate
Benzonatate Capsules
Benzphetamine Hydrochloride
Benzphetamine Hydrochloride Tablets
Benzthiazide
Benzthiazide Tablets
Benzyl Alcohol
Benzyl Benzoate Lotion
Betamethasone
Betamethasone Cream
Betamethasone Tablets
Betamethasone Acetate
Betamethasone Sodium Phosphate
Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension, Sterile
Betamethasone Valerate
Betamethasone Valerate Cream
Biperiden
Biperiden Hydrochloride
Biperiden Hydrochloride Tablets
Biperiden Lactate Injection
Bisacodyl
Bisacodyl Suppositories
Bisacodyl Tablets
Bishydroxycoumarin Capsules
Bismuth, Milk of
Bismuth Subnitrate
Blood Group Specific Substances A and B
Boric Acid
Bromodiphenhydramine Hydrochloride
Bromodiphenhydramine Hydrochloride Capsules

Bromodiphenhydramine Hydrochloride Elixir
Brompheniramine Maleate
Brompheniramine Maleate Elixir
Brompheniramine Maleate Tablets
Butalbital
Butethamine Hydrochloride
Butethamine Hydrochloride and Epinephrine Injection
Butyl Aminobenzoate

C

Caffeine, Citrated
Caffeine, Citrated, Tablets
Calcium Aminosalicylate
Calcium Aminosalicylate Capsules
Calcium Aminosalicylate Tablets
Calcium Benzoylpas
Calcium Benzoylpas Tablets
Calcium Carbonate Tablets
Calcium Cyclamate
Calcium Cyclamate and Calcium Saccharin Solution
Calcium Cyclamate and Calcium Saccharin Tablets
Calcium Ipodate
Calcium Ipodate for Oral Suspension
Calcium Lactate
Calcium Lactate Tablets
Calcium Novobiocin
Calcium Novobiocin Oral Suspension
Calcium Oxytetracycline
Calcium Oxytetracycline Oral Suspension
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Saccharin
Calcium Stearate
Calcium Sulfate
Camphor Spirit
Camphorated Parachlorophenol
Candicidin
Candicidin Ointment
Candicidin Suppositories
Caramel
Caraway
Caraway Oil
Carbarsone
Carbarsone Capsules
Carbarsone Tablets
Carbetapentane Citrate
Carbinoxamine Maleate
Carbinoxamine Maleate Elixir
Carbinoxamine Maleate Tablets
Carbol-Fuchsin Solution
Cardamom Seed
Cardamom Tincture, Compound
Carphenazine Maleate
Carphenazine Maleate Tablets
Cascara Tablets
Cascara Sagrada Extract
Cascara Sagrada Fluidextract
Castor Oil, Aromatic
Cellulose, Microcrystalline
Cetyl Alcohol
Cetylpyridinium Chloride
Cetylpyridinium Chloride Solution
Chloral Betaine
Chloral Betaine Tablets
Chloramphenicol for Suspension, Sterile
Chlorcyclizine Hydrochloride
Chlorcyclizine Hydrochloride Tablets
Chlordiazepoxide
Chlordiazepoxide Tablets
Chlormadinone Acetate
Chlormadinone Acetate and Mestranol Tablets
Chlormerodrin
Chlormerodrin Tablets
Chloroform
Chloroprocaine Hydrochloride
Chloroprocaine Hydrochloride Injection
Chlorothen Citrate
Chlorothen Citrate Tablets
Chlorothiazide
Chlorothiazide Tablets
Chlorothiazide Oral Suspension
Chlorotrianisene
Chlorotrianisene Capsules
Chlorpheniramine Maleate Injection
Chlorprothixene
Chlorprothixene Tablets
Chlortetracycline Hydrochloride
Chlortetracycline Hydrochloride Capsules
Chlortetracycline Hydrochloride for Injection
Chlortetracycline Hydrochloride, Ophthalmic
Chymotrypsin
Chymotrypsin, Sterile
Chymotrypsin Injection
Cinnamon
Clidinium Bromide
Clofibrate
Clofibrate Capsules
Cobalamin Concentrate
Cocaine
Cocaine Hydrochloride Tablets
Codeine
Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets
Codeine Sulfate
Codeine Sulfate Tablets
Cod Liver Oil
Cod Liver Oil, Nondestearinated
Colistin Sulfate
Colistin Sulfate for Oral Suspension
Cresol
Cresol Solution, Saponated
Cupric Sulfate
Cyanocobalamin Co 60 Capsules
Cyanocobalamin Co 60 Solution
Cyclopentamine Hydrochloride
Cyclopentamine Hydrochloride Injection
Cyclopentamine Hydrochloride Solution
Cyclothiazide
Cyclothiazide Tablets
Cycrimine Hydrochloride
Cycrimine Hydrochloride Tablets
Cyproheptadine Hydrochloride
Cyproheptadine Hydrochloride Syrup
Cyproheptadine Hydrochloride Tablets

D

Danthron
Danthron Tablets
Dehydrocholic Acid
Dehydrocholic Acid Tablets
Demeclocycline
Demeclocycline for Oral Suspension
Demeclocycline Oral Suspension
Demeclocycline Hydrochloride
Demeclocycline Hydrochloride Capsules
Demeclocycline Hydrochloride Tablets
Denatonium Benzoate
Desipramine Hydrochloride
Desipramine Hydrochloride Capsules
Desipramine Hydrochloride Tablets
Desoxycorticosterone Acetate Pellets
Desoxycorticosterone Pivalate
Desoxycorticosterone Pivalate Suspension, Sterile
Dexamethasone Aerosol
Dexamethasone Elixir
Dexamethasone Sodium Phosphate Cream
Dexamethasone Sodium Phosphate Ophthalmic Ointment
Dexamethasone Sodium Phosphate Ophthalmic Solution
Dexbrompheniramine Maleate
Dexbrompheniramine Maleate Tablets
Dexchlorpheniramine Maleate
Dexchlorpheniramine Maleate Syrup
Dexchlorpheniramine Maleate Tablets
Dextriferron Injection
Dextroamphetamine Phosphate
Dextroamphetamine Phosphate Tablets
Dextromethorphan Hydrobromide
Dextromethorphan Hydrobromide Syrup
Diazepam
Diazepam Injection
Diazepam Tablets
Dibucaine
Dibucaine Cream
Dibucaine Ointment
Dichlorodifluoromethane
Dichlorotetrafluoroethane
Dicyclomine Hydrochloride
Dicyclomine Hydrochloride Capsules
Dicyclomine Hydrochloride Syrup
Dienestrol
Dienestrol Cream
Dienestrol Tablets
Diethylpropion Hydrochloride
Diethylpropion Hydrochloride Tablets
Diethylstilbestrol Dipropionate
Diethylstilbestrol Dipropionate Tablets
Digitalis Capsules
Digitoxin Injection
Dihydroxyaluminum Aminoacetate
Dihydroxyaluminum Aminoacetate Magma
Dihydroxyaluminum Aminoacetate Tablets
Dihydroxyaluminum Sodium Carbonate
Dihydroxyaluminum Sodium Carbonate Tablets
Dimethindene Maleate
Dimethindene Maleate Syrup
Dimethindene Maleate Tablets
Dimethisoquin Hydrochloride
Dimethisoquin Hydrochloride Lotion
Dimethisoquin Hydrochloride Ointment
Dimethisterone
Dimethyl Tubocurarine Iodide
Dimethyl Tubocurarine Iodide Injection
Dioctyl Calcium Sulfosuccinate
Dioctyl Calcium Sulfosuccinate Capsules
Dioctyl Sodium Sulfosuccinate Solution
Dioctyl Sodium Sulfosuccinate Syrup
Diphemanil Methylsulfate
Diphemanil Methylsulfate Injection
Diphemanil Methylsulfate Tablets
Diphenadione
Diphenadione Tablets
Diphenylhydantoin Oral Suspension
Diphenoxylate Hydrochloride
Diphenoxylate Hydrochloride and Atropine Sulfate Solution
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets
Doxapram Hydrochloride
Doxapram Hydrochloride Injection
Dromostanolone Propionate
Dromostanolone Propionate Injection
Dydrogesterone
Dydrogesterone Tablets

E

Ephedrine
Ephedrine Hydrochloride
Ephedrine Sulfate and Phenobarbital Capsules
Ephedrine Sulfate Tablets
Ergotamine Tartrate and Caffeine Suppositories
Ergotamine Tartrate and Caffeine Tablets
Eriodictyon
Eriodictyon Fluidextract
Eriodictyon Syrup, Aromatic
Erythrityl Tetranitrate, Diluted
Erythrityl Tetranitrate Tablets
Erythromycin Estolate
Erythromycin Estolate Capsules
Erythromycin Estolate for Oral Suspension
Erythromycin Estolate Tablets
Erythromycin Ethylsuccinate
Erythromycin Ethylsuccinate Injection
Erythromycin Ethylsuccinate for Oral Suspension
Erythromycin Ethylsuccinate Tablets
Estradiol
Estradiol Pellets
Estradiol Suspension, Sterile
Estradiol Tablets
Estradiol Benzoate
Estradiol Benzoate Injection
Estradiol Cypionate
Estradiol Cypionate Injection
Estradiol Dipropionate

Estradiol Dipropionate Injection
Estrone
Estrone Injection
Ethamivan
Ethamivan Injection
Ethchlorvynol
Ethchlorvynol Capsules
Ethinamate
Ethinamate Tablets
Ethinyl Estradiol and Dimethisterone Tablets
Ethisterone
Ethisterone Tablets
Ethoheptazine Citrate
Ethoheptazine Citrate Tablets
Ethyl Acetate
Ethyl Biscoumacetate
Ethyl Biscoumacetate Tablets
Ethyl Chloride
Ethylcellulose
Ethylene
Ethylmorphine Hydrochloride
Ethyl Vanillin
Eucalyptus Oil

F

Ferrous Gluconate
Ferrous Gluconate Tablets
Ferrous Sulfate Syrup
Fluocinolone Acetonide
Fluorometholone
Fluorometholone Cream
Fluphenazine Enanthate
Fluphenazine Enanthate Injection
Fluphenazine Hydrochloride
Fluphenazine Hydrochloride Injection
Fluphenazine Hydrochloride Tablets
Fluprednisolone
Fluprednisolone Tablets
Flurandrenolide
Flurandrenolide Cream
Flurandrenolide Ointment
Flurothyl
Fluroxene
Fructose
Fructose Injection
Fructose and Sodium Chloride Injection
Fuchsin, Basic
Furazolidone
Furazolidone and Nifuroxime Powder
Furazolidone and Nifuroxime Suppositories

G

Gitalin
Gitalin Tablets
Glutamic Acid Hydrochloride
Glutamic Acid Hydrochloride Capsules
Glutethimide
Glutethimide Tablets
Glycerin Suppositories
Glyceryl Guaiacolate
Glyceryl Guaiacolate Syrup
Glyceryl Monostearate
Glycobiarsol
Glycobiarsol Tablets
Glycopyrrolate
Glycopyrrolate Tablets
Gramicidin
Green Soap
Green Soap Tincture

H

Haloperidol
Haloperidol Solution
Haloperidol Tablets
Hexavitamin Capsules
Hexavitamin Tablets
Hexylcaine Hydrochloride
Hexylcaine Hydrochloride Injection
Hexylcaine Hydrochloride Solution
Hexylresorcinol
Hexylresorcinol Pills
Homatropine Methylbromide
Homatropine Methylbromide Tablets
Hyaluronidase for Injection
Hydralazine Hydrochloride
Hydralazine Hydrochloride Injection
Hydralazine Hydrochloride Tablets
Hydrochloric Acid, Diluted
Hydrocortisone Lotion
Hydroflumethiazide
Hydroflumethiazide Tablets
Hydromorphone Hydrochloride
Hydromorphone Hydrochloride Injection
Hydromorphone Hydrochloride Tablets
Hydroquinone
Hydroquinone Ointment
Hydroxypropyl Methylcellulose
Hydroxyzine Hydrochloride
Hydroxyzine Hydrochloride Injection
Hydroxyzine Hydrochloride Syrup
Hydroxyzine Hydrochloride Tablets
Hydroxyzine Pamoate
Hydroxyzine Pamoate Capsules
Hydroxyzine Pamoate Oral Suspension
Hyoscyamine Hydrobromide
Hyoscyamine Sulfate
Hyoscyamine Sulfate Tablets
Hypophosphorous Acid

I

Ichthammol
Ichthammol Ointment
Indomethacin
Indomethacin Capsules
Iodine Ampuls
Iodine Solution
Iodized Oil
Iodochlorhydroxyquin and Hydrocortisone Cream
Iodochlorhydroxyquin and Hydrocortisone Lotion
Iodochlorhydroxyquin and Hydrocortisone Ointment
Iodochlorhydroxyquin Powder, Compound
Iodochlorhydroxyquin Tablets
Iodoform
Iodopyracet Injection
Iso-alcoholic Elixir

Isobucaine Hydrochloride
Isobucaine Hydrochloride and Epinephrine Injection
Isocarboxazid
Isocarboxazid Tablets
Isoflurophate Ophthalmic Ointment
Isopropamide Iodide
Isopropamide Iodide Tablets
Isopropyl Alcohol
Isopropyl Rubbing Alcohol
Isoproterenol Sulfate Aerosol
Isoxsuprine Hydrochloride
Isoxsuprine Hydrochloride Tablets

J

Juniper Tar

K

Kaolin
Kaolin Mixture with Pectin

L

Lanatoside C
Lanatoside C Tablets
Lavender Oil
Levonordefrin
Levopropoxyphene Napsylate
Levopropoxyphene Napsylate Capsules
Levorphanol Tartrate
Levorphanol Tartrate Injection
Levorphanol Tartrate Tablets

M

Magaldrate
Magaldrate Oral Suspension
Magaldrate Tablets
Magnesium Carbonate
Magnesium Citrate Solution
Magnesium Hydroxide
Magnesium Phosphate
Menadiol Sodium Diphosphate Tablets
Menadione
Menadione Injection
Menadione Tablets
Menadione Sodium Bisulfite
Menadione Sodium Bisulfite Injection
Mepenzolate Bromide
Mepenzolate Bromide Tablets
Meperidine Hydrochloride Syrup
Mephobarbital
Mephobarbital Tablets
Mepivacaine Hydrochloride
Mepivacaine Hydrochloride Injection
Mepivacaine Hydrochloride and Levonordefrin Injection
Meprobamate Oral Suspension
Meprylcaine Hydrochloride
Meprylcaine Hydrochloride and Epinephrine Injection
Mercuric Oxide, Yellow
Mercuric Oxide Ophthalmic Ointment, Yellow
Mestranol Tablets
Metabutethamine Hydrochloride
Metabutethamine Hydrochloride and Epinephrine Injection
Methacholine Bromide
Methacholine Bromide Tablets
Methacholine Chloride
Methacholine Chloride, Sterile
Methacycline Hydrochloride
Methacycline Hydrochloride Capsules
Methacycline Hydrochloride Oral Suspension
Methandrostenolone
Methandrostenolone Tablets
Methantheline Bromide
Methantheline Bromide Tablets
Methapyrilene Hydrochloride
Methapyrilene Hydrochloride Capsules
Methapyrilene Hydrochloride Tablets
Metharbital
Metharbital Tablets
Methdilazine
Methdilazine Tablets
Methdilazine Hydrochloride
Methdilazine Hydrochloride Syrup
Methdilazine Hydrochloride Tablets
Methenamine
Methenamine Tablets
Methenamine and Sodium Biphosphate Tablets
Methionine
Methionine Capsules
Methionine Tablets
Methocarbamol
Methocarbamol Injection
Methocarbamol Tablets
Methotrimeprazine
Methotrimeprazine Injection
Methoxyflurane
Methscopolamine Bromide
Methscopolamine Bromide Injection
Methscopolamine Bromide Tablets
Methsuximide
Methsuximide Capsules
Methyclothiazide
Methyclothiazide Tablets
Methylbenzethonium Chloride
Methylbenzethonium Chloride Powder
Methyl Isobutyl Ketone
Methylprednisolone
Methylprednisolone Tablets
Methylprednisolone Acetate
Methylprednisolone Acetate Suspension, Sterile
Methylprednisolone Sodium Succinate
Methylprednisolone Sodium Succinate for Injection
Methyltestosterone
Methyltestosterone Tablets
Methylthiouracil
Methyprylon
Methyprylon Capsules
Methyprylon Tablets
Methysergide Maleate
Methysergide Maleate Tablets
Mineral Oil Emulsion
Mineral Oil, Light
Monobenzone
Monobenzone Lotion
Monobenzone Ointment
Monoethanolamine
Morphine and Atropine Sulfates Tablets
Myristica Oil

N

Nalidixic Acid
Nalidixic Acid Tablets
Nandrolone Decanoate
Nandrolone Decanoate Injection
Nandrolone Phenpropionate
Nandrolone Phenpropionate Injection
Naphazoline Hydrochloride
Naphazoline Hydrochloride Solution
Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream
Neomycin Sulfate and Hydrocortisone Acetate Lotion
Neomycin Sulfate, Polymyxin B Sulfate, and Gramicidin Ophthalmic Solution
Neomycin Sulfate, Polymyxin B Sulfate, and Zinc Bacitracin Ointment
Niacin
Niacin Injection
Niacin Tablets
Nialamide
Nialamide Tablets
Nifuroxime
Nikethamide
Nikethamide Injection
Nitrofurazone
Nitrofurazone Cream
Nitrofurazone Ointment
Nitrofurazone Solution
Nitromersol
Nitromersol Solution
Nitromersol Tincture
Norethandrolone
Norethandrolone Tablets
Norethindrone Acetate
Norethindrone Acetate Tablets
Norethindrone Tablets
Nortriptyline Hydrochloride
Nortriptyline Hydrochloride Capsules
Noscapine
Nylidrin Hydrochloride
Nylidrin Hydrochloride Injection
Nylidrin Hydrochloride Tablets

O

Octoxynol
Ointment, Yellow
Oleandomycin Phosphate
Oleandomycin Phosphate, Sterile
Oleovitamin A and D
Oleovitamin A and D Capsules
Orange Flower Oil
Orange Flower Water
Orange Peel, Bitter
Orphenadrine Citrate
Oxandrolone
Oxandrolone Tablets
Oxazepam
Oxazepam Capsules
Oxtriphylline
Oxtriphylline Tablets
Oxymetazoline Hydrochloride
Oxymetazoline Hydrochloride Solution
Oxymetholone
Oxymetholone Tablets
Oxymorphone Hydrochloride
Oxymorphone Hydrochloride Injection
Oxymorphone Hydrochloride Tablets
Oxyphenbutazone
Oxyphenbutazone Tablets
Oxyphencyclimine Hydrochloride
Oxyphencyclimine Hydrochloride Tablets
Oxytetracycline Hydrochloride, Ophthalmic
Oxytetracycline Injection

P

Pancreatin
Papaverine Hydrochloride
Papaverine Hydrochloride Injection
Papaverine Hydrochloride Tablets
Parachlorophenol
Paraffin
Paramethasone Acetate
Paramethasone Acetate Tablets
Pargyline Hydrochloride
Pargyline Hydrochloride Tablets
Paromomycin Sulfate
Paromomycin Sulfate Capsules
Pectin
Pentaerythritol Tetranitrate, Diluted
Pentaerythritol Tetranitrate Tablets
Pentazocine
Pentazocine Lactate Injection
Penthienate Bromide
Penthienate Bromide Tablets
Pentylenetetrazol
Pentylenetetrazol Injection
Peppermint Spirit
Peppermint Water
Perphenazine
Perphenazine Injection
Perphenazine Tablets
Persic Oil
Peruvian Balsam
Petrolatum
Phenacaine Hydrochloride
Phenazopyridine Hydrochloride
Phenazopyridine Hydrochloride Tablets
Phenindamine Tartrate
Phenindamine Tartrate Tablets
Phenmetrazine Hydrochloride
Phenmetrazine Hydrochloride Tablets
Phenolphthalein
Phenolphthalein Tablets
Phenprocoumon
Phenprocoumon Tablets
Phensuximide
Phensuximide Capsules
Phensuximide Oral Suspension
Phentolamine Hydrochloride
Phentolamine Hydrochloride Tablets
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
Phenylpropanolamine Hydrochloride
Phosphoric Acid
Phosphoric Acid, Diluted
Phthalylsulfacetamide
Phthalylsulfacetamide Tablets
Phthalylsulfathiazole
Phthalylsulfathiazole Tablets

Picrotoxin
Picrotoxin Injection
Piminodine Esylate
Piminodine Esylate Injection
Piminodine Esylate Tablets
Pine Needle Oil
Pine Tar
Pipobroman
Pipobroman Tablets
Plantago Seed
Polycarbophil
Polyethylene Glycol 300
Polyethylene Glycol 1540
Polymyxin B Sulfate Tablets
Polythiazide
Polythiazide Tablets
Posterior Pituitary
Posterior Pituitary Injection
Potash, Sulfurated
Potassic Saline Injection, Lactated
Potassium Acetate
Potassium Citrate
Potassium Gluconate
Potassium Gluconate Elixir
Potassium Gluconate Tablets
Potassium Guaiacolsulfonate
Potassium Iodide Solution
Potassium Phenethicillin
Potassium Phenethicillin for Oral Solution
Potassium Phenethicillin Tablets
Potassium Phosphate, Monobasic
Potassium Sodium Tartrate
Potassium Sorbate
Potassium Warfarin
Potassium Warfarin Tablets
Povidone
Povidone-Iodine
Povidone-Iodine Aerosol
Povidone-Iodine Solution
Pramoxine Hydrochloride
Pramoxine Hydrochloride Cream
Pramoxine Hydrochloride Jelly
Prednisolone Succinate
Prednisolone Sodium Succinate for Injection
Prilocaine Hydrochloride
Prilocaine Hydrochloride Injection
Procaine Hydrochloride and Levonordefrin Injection
Procaine and Phenylephrine Hydrochlorides Injection
Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection
Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection
Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection
Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection
Procaine, Tetracaine, and Phenylephrine Hydrochlorides Injection
Procaine Penicillin G and Sodium Penicillin G for Injection
Prochlorperazine
Prochlorperazine Suppositories
Progesterone
Progesterone Injection
Progesterone Suspension, Sterile
Progesterone Tablets
Promazine Hydrochloride
Promazine Hydrochloride Injection
Promazine Hydrochloride Syrup
Promazine Hydrochloride Tablets
Propiomazine Hydrochloride
Propiomazine Hydrochloride Injection
Propoxycaine Hydrochloride
Propoxycaine Hydrochloride Injection
Propoxyphene Hydrochloride and Aspirin Capsules
Propylhexedrine
Propylhexedrine Inhalant
Pseudoephedrine Hydrochloride
Pseudoephedrine Hydrochloride Syrup
Pseudoephedrine Hydrochloride Tablets
Pumice
Pyrilamine Maleate
Pyrilamine Maleate Tablets
Pyrrobutamine Phosphate
Pyrrobutamine Phosphate Tablets
Pyrrocaine Hydrochloride
Pyrrocaine Hydrochloride and Epinephrine Injection

Q

Quinine Dihydrochloride
Quinine Dihydrochloride Injection

R

Rauwolfia Serpentina
Rauwolfia Serpentina, Powdered
Rauwolfia Serpentina Tablets
Rescinnamine
Rescinnamine Tablets
Resorcinol Monoacetate
Resorcinol Ointment, Compound
Ringer's Solution
Rolitetracycline
Rolitetracycline for Injection
Rose Oil
Rose Water, Stronger
Rose Water Ointment
Rosin

S

Salicylamide
Salicylamide Oral Suspension
Salicylamide Tablets
Salicylanilide
Selenium Sulfide
Selenium Sulfide Detergent Suspension
Senna
Senna Fluidextract
Senna Syrup
Silicon Dioxide, Colloidal
Silver Protein, Mild
Sitosterols
Sitosterols Suspension
Sodium Acetate
Sodium Alginate
Sodium Biphosphate
Sodium Butabarbital
Sodium Butabarbital Capsules
Sodium Butabarbital Elixir
Sodium Butabarbital Tablets

Sodium Carboxymethylcellulose Tablets
Sodium Chloride and Dextrose Tablets
Sodium Chlorothiazide for Injection
Sodium Citrate Solution, Anticoagulant
Sodium Cyclamate
Sodium Cyclamate and Sodium Saccharin Solution
Sodium Cyclamate and Sodium Saccharin Tablets
Sodium Dehydrocholate Injection
Sodium Dextrothyroxine
Sodium Dextrothyroxine Tablets
Sodium Hypochlorite Solution
Sodium Hypochlorite Solution, Diluted
Sodium Ipodate
Sodium Ipodate Capsules
Sodium Methiodal
Sodium Methiodal Injection
Sodium Methohexital for Injection
Sodium Novobiocin
Sodium Novobiocin Capsules
Sodium Novobiocin for Injection
Sodium Penicillin G
Sodium Penicillin G for Injection
Sodium Phosphate
Sodium Phosphate, Dried
Sodium Phosphate, Effervescent
Sodium Phosphate Solution
Sodium Propionate
Sodium Saccharin
Sodium Saccharin Tablets
Sodium Secobarbital and Sodium Amobarbital Capsules
Sodium Stearate
Sodium Thiamylal for Injection
Sodium Vinbarbital Injection
Sorbic Acid
Spearmint
Spearmint Oil
Stannous Fluoride
Stanozolol
Stanozolol Tablets
Starch Glycerite
Sucrose Octaacetate
Sulfacetamide
Sulfacetamide Tablets
Sulfacetamide, Sulfadiazine and Sulfamerazine Oral Suspension
Sulfacetamide, Sulfadiazine and Sulfamerazine Tablets
Sulfadiazine and Sulfamerazine Tablets
Sulfadimethoxine
Sulfadimethoxine Oral Suspension
Sulfadimethoxine Tablets
Sulfaethidole
Sulfamerazine Tablets
Sulfamethizole
Sulfamethizole Oral Suspension
Sulfamethizole Tablets
Sulfamethoxazole
Sulfamethoxazole Oral Suspension
Sulfamethoxazole Tablets
Sulfisoxazole and Phenazopyridine Hydrochloride Tablets
Sulfur, Sublimed
Syrosingopine
Syrosingopine Tablets

T

Tartaric Acid
Terpin Hydrate
Terpin Hydrate Elixir
Terpin Hydrate and Codeine Elixir
Terpin Hydrate and Dextromethorphan Elixir
Testosterone
Testosterone Pellets
Testosterone Suspension, Sterile
Tetanus and Gas Gangrene Antitoxins
Tetracaine
Tetracaine Ophthalmic Ointment
Tetracycline Hydrochloride for Ophthalmic Solution
Tetracycline Hydrochloride Tablets
Tetracycline Phosphate Complex
Tetracycline Phosphate Complex Capsules
Tetrahydrozoline Hydrochloride
Tetrahydrozoline Hydrochloride Ophthalmic Solution
Tetrahydrozoline Hydrochloride Solution
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets
Theophylline Tablets
Theophylline Sodium Acetate
Theophylline Sodium Acetate Tablets
Theophylline Sodium Glycinate
Theophylline Sodium Glycinate Tablets
Thiethylperazine Maleate
Thiethylperazine Maleate Tablets
Thihexinol Methylbromide
Thimerosal
Thimerosal Aerosol
Thimerosal Solution
Thimerosal Tincture
Thioguanine
Thioguanine Tablets
Thiopropazate Hydrochloride
Thiopropazate Hydrochloride Tablets
Thrombin
Tolu Balsam Syrup
Tolu Balsam Tincture
Tranylcypromine Sulfate
Tranylcypromine Sulfate Tablets
Triacetin
Triacetin Aerosol
Triacetin Cream
Triacetin Powder
Triamcinolone Acetonide Aerosol
Triamcinolone Diacetate
Triamcinolone Diacetate Suspension, Sterile
Triamcinolone Diacetate Syrup
Tribromoethanol
Tribromoethanol Solution
Trichlormethiazide
Trichlormethiazide Tablets
Trichloromonofluoromethane
Triclobisonium Chloride
Triclobisonium Chloride Cream
Triclobisonium Chloride Ointment
Tridihexethyl Chloride
Tridihexethyl Chloride Tablets
Triethylenemelamine
Triethylenemelamine Tablets
Trifluoperazine Hydrochloride

Trifluoperazine Hydrochloride Injection
Trifluoperazine Hydrochloride Tablets
Triflupromazine Hydrochloride
Triflupromazine Hydrochloride Tablets
Trimeprazine Tartrate
Trimeprazine Tartrate Syrup
Trimeprazine Tartrate Tablets
Trimethadione Tablets
Trimethidinium Methosulfate
Trimethidinium Methosulfate Tablets
Trimethobenzamide Hydrochloride
Trimethobenzamide Hydrochloride Capsules
Trimethobenzamide Hydrochloride Injection
Trimethobenzamide Hydrochloride and Benzocaine Suppositories
Trioxsalen
Trioxsalen Tablets
Triprolidine Hydrochloride
Triprolidine Hydrochloride Tablets
Troleandomycin
Troleandomycin Capsules
Troleandomycin Oral Suspension
Tromethamine
Tromethamine for Injection
Trypsin Crystallized
Tuaminoheptane Sulfate
Tuaminoheptane Sulfate Solution
Tybamate
Tybamate Capsules
Tyrothricin

U

Undecylenic Acid
Undecylenic Acid Ointment, Compound
Urethan
Urethan Tablets

V

Valethamate Bromide
Valethamate Bromide Injection
Vanilla
Vanilla Tincture
Vinbarbital
Vinbarbital Capsules
Vinyl Ether
Vitamin E

W

Wax, Yellow
White Lotion

X

Xylometazoline Hydrochloride
Xylometazoline Hydrochloride Solution

Y

Yeast, Dried
Yeast, Dried, Tablets

Z

Zinc-Eugenol Cement
Zinc Oxide Paste with Salicylic Acid
Zinc Undecylenate

Classification of NF XIII Articles by Pharmacological Categories*

Abrasive (Dental)
- Pumice

Absorbent (Gastrointestinal)
- Polycarbophil

Acidifier

Acidifier (Gastric)
- Glutamic Acid Hydrochloride
- Hydrochloric Acid, Diluted

Acidifier (Urinary)
- Sodium Biphosphate

Adrenergic
- Pseudoephedrine Hydrochloride
- Tuaminoheptane Sulfate

Adrenergic (Bronchodilator)
- Ephedrine
- Ephedrine Hydrochloride
- Ephedrine Sulfate and Phenobarbital [Capsules]
- Ephedrine Sulfate [Tablets]
- Isoproterenol Sulfate [Aerosol]

Adrenergic (Ophthalmic)

Adrenergic (Vasoconstrictor)
- Cyclopentamine Hydrochloride
- Levonordefrin
- Naphazoline Hydrochloride
- Oxymetazoline Hydrochloride
- Phenylpropanolamine Hydrochloride
- Propylhexedrine
- Tetrahydrozoline Hydrochloride
- Xylometazoline Hydrochloride

Adrenergic (Vasopressor)

Adsorbent
- Kaolin
- Kaolin Mixture with Pectin

Alkalizer
- Potassium Acetate
- Potassium Citrate
- Tromethamine

Alkalizer (Urinary)
- Sodium Acetate

Analgesic
- Acetaminophen
- Aluminum Aspirin
- Antipyrine
- Aspirin [Capsules]
- Aspirin, Phenacetin and Caffeine [Tablets]
- Ethoheptazine Citrate
- Methotrimeprazine
- Pentazocine
- Pentazocine Lactate [Injection]
- Propoxyphene Hydrochloride and Aspirin [Capsules]
- Salicylamide

Analgesic (Dental)

Analgesic (Narcotic)
- Alphaprodine Hydrochloride
- Anileridine
- Anileridine Hydrochloride
- Codeine
- Codeine Phosphate, Aspirin, Phenacetin, and Caffeine [Tablets]
- Codeine Sulfate
- Hydromorphone Hydrochloride
- Levorphanol Tartrate
- Meperidine Hydrochloride [Syrup]
- Morphine and Atropine Sulfate [Tablets]
- Oxymorphone Hydrochloride
- Piminodine Esylate

Analgesic (Urinary Tract)
- Phenazopyridine Hydrochloride
- Sulfisoxazole and Phenazopyridine Hydrochloride [Tablets]

Androgen
- Methandrostenolone
- Methyltestosterone
- Nandrolone Decanoate
- Nandrolone Phenpropionate
- Norethandrolone
- Oxandrolone
- Oxymetholone
- Stanozolol
- Testosterone

Anesthetic, General (Inhalation)
- Ethylene
- Fluroxene
- Methoxyflurane
- Vinyl Ether

Anesthetic, General (Systemic)
- Sodium Methohexital [for Injection]
- Sodium Thiamylal [for Injection]
- Tribromoethanol

Anesthetic, Local
- Antipyrine and Benzocaine [Solution]
- Benzocaine
- Butyl Aminobenzoate
- Chloroprocaine Hydrochloride
- Dibucaine
- Dimethisoquin Hydrochloride
- Ethyl Chloride
- Hexylcaine Hydrochloride

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* This list of category statements has been developed in order to provide a comprehensive classification system. Article titles are listed only under the category statements describing the therapeutic or pharmaceutic basis for recognition of articles finally admitted to NF XIII. Although some category statements do not include any of the articles finally admitted to NF XIII, they have been retained in this listing as a matter of information.

- Isobucaine Hydrochloride
- Isobucaine Hydrochloride and Epinephrine [Injection]
- Mepivacaine Hydrochloride
- Mepivacaine Hydrochloride and Levonordefrin [Injection]
- Meprylcaine Hydrochloride
- Meprylcaine Hydrochloride and Epinephrine [Injection]
- Pramoxine Hydrochloride
- Prilocaine Hydrochloride
- Propoxycaine Hydrochloride
- Tetracaine

Anesthetic, Local (Dental)

- Butethamine Hydrochloride
- Butethamine Hydrochloride and Epinephrine [Injection]
- Metabutethamine Hydrochloride
- Metabutethamine Hydrochloride and Epinephrine [Injection]
- Procaine Hydrochloride and Levonordefrin [Injection]
- Procaine and Phenylephrine Hydrochlorides [Injection]
- Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate [Injection]
- Procaine and Propoxycaine Hydrochlorides and Levonordefrin [Injection]
- Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate [Injection]
- Procaine and Tetracaine Hydrochlorides and Levonordefrin [Injection]
- Procaine, Tetracaine and Phenylephrine Hydrochlorides [Injection]
- Pyrrocaine Hydrochloride
- Pyrrocaine Hydrochloride and Epinephrine [Injection]

Anesthetic, Local (Narcotic)

- Cocaine

Anesthetic, Local (Ophthalmic)

- Phenacaine Hydrochloride

Anorexic

- Benzphetamine Hydrochloride
- Diethylpropion Hydrochloride
- Phenmetrazine Hydrochloride

Antacid

- Aluminum Phosphate [Gel]
- Bismuth, Milk of
- Bismuth Subnitrate
- Calcium Carbonate [Tablets]
- Dihydroxyaluminum Aminoacetate
- Dihydroxyaluminum Sodium Carbonate
- Magaldrate
- Magnesium Carbonate
- Magnesium Hydroxide
- Magnesium Phosphate

Anthelmintic

Anthelmintic (Filariae)

Anthelmintic (Intestinal Roundworms and Trematodes)

- Hexylresorcinol

Anthelmintic (Schistosomes)

Antiadrenergic

- Phentolamine Hydrochloride

Antiadrenergic—Central Stimulant (Specific Analgesic for Migraine)

- Ergotamine Tartrate and Caffeine [Suppositories and Tablets]

Antiadrenergic (Migraine Prophylactic)

- Methysergide Maleate

Antiamebic

- Carbarsone
- Glycobiarsol
- Iodochlorhydroxyquin [Tablets]
- Paromomycin Sulfate

Antiandrogen

Antiarthritic

- Oxyphenbutazone

Antibacterial

- Acetyl Sulfisoxazole
- Calcium Novobiocin
- Calcium Oxytetracycline
- Chloramphenicol [for Suspension, Sterile]
- Chlortetracycline Hydrochloride
- Demeclocycline
- Demeclocycline Hydrochloride
- Erythromycin Estolate
- Erythromycin Ethylsuccinate
- Gramicidin
- Methacycline Hydrochloride
- Nalidixic Acid
- Neomycin Sulfate and Hydrocortisone Acetate [Lotion]
- Oleandomycin Phosphate
- Oxytetracycline Hydrochloride [Ophthalmic]
- Oxytetracycline [Injection]
- Potassium Phenethicillin
- Procaine Penicillin G and Sodium Penicillin G [for Injection]
- Rolitetracycline
- Sodium Novobiocin
- Sodium Penicillin G
- Sulfacetamide
- Sulfacetamide, Sulfadiazine, and Sulfamerazine [Oral Suspension and Tablets]
- Sulfadiazine and Sulfamerazine [Tablets]
- Sulfadimethoxine
- Sulfaethidole
- Sulfamerazine [Tablets]
- Sulfamethizole
- Sulfamethoxazole
- Sulfisoxazole and Phenazopyridine Hydrochloride [Tablets]
- Tetracycline Hydrochloride [for Ophthalmic Solution]
- Tetracycline Hydrochloride [Tablets]
- Tetracycline Phosphate Complex
- Troleandomycin
- Tyrothricin

Antibacterial (Intestinal)
- Colistin Sulfate
- Phthalylsulfacetamide
- Phthalylsulfathiazole
- Polymyxin B Sulfate [Tablets]

Antibacterial (Leprostatic)

Antibacterial (Tuberculostatic)
- Calcium Aminosalicylate
- Calcium Benzoylpas

Antibacterial (Urinary)
- Methenamine
- Methenamine and Sodium Biphosphate [Tablets]

Anticholesteremic
- Clofibrate
- Sitosterols
- Sodium Dextrothyroxine

Anticholinergic
- Alverine Citrate
- Atropine
- Belladonna [Extract]
- Belladonna Leaf [Fluidextract]
- Biperiden
- Biperiden Hydrochloride
- Biperiden Lactate [Injection]
- Clidinium Bromide
- Cycrimine Hydrochloride
- Dicyclomine Hydrochloride
- Diphemanil Methylsulfate
- Glycopyrrolate
- Homatropine Methylbromide
- Hyoscyamine Hydrobromide
- Hyoscyamine Sulfate
- Isopropamide Iodide
- Mepenzolate Bromide
- Methantheline Bromide
- Methscopolamine Bromide
- Morphine and Atropine Sulfates [Tablets]
- Oxyphencyclimine Hydrochloride
- Penthienate Bromide
- Thihexinol Methylbromide
- Tridihexethyl Chloride
- Valethamate Bromide

Anticholinergic (Ophthalmic)

Anticholinesterase (Curare Principles Antidote)

Anticoagulant
- Anisindione
- Bishydroxycoumarin [Capsules]
- Diphenadione
- Ethyl Biscoumacetate
- Phenprocoumon
- Potassium Warfarin

Anticoagulant for Plasma and for Blood for Fractionation
- Sodium Citrate [Solution, Anticoagulant]

Anticonvulsant
- Diphenylhydantoin [Oral Suspension]
- Mephobarbital
- Metharbital
- Methsuximide
- Phensuximide
- Trimethadione [Tablets]

Antidepressant
- Desipramine Hydrochloride
- Isocarboxazid
- Nialamide
- Nortriptyline Hydrochloride
- Tranylcypromine Sulfate

Antidiarrheal (Narcotic)
- Diphenoxylate Hydrochloride
- Diphenoxylate Hydrochloride and Atropine Sulfate [Solution and Tablets]

Antidiuretic

Antidote (Heparin)

Antidote (Narcotic Analgesics)

Antidote (Phosphorus)
- Cupric Sulfate

Antieczematic, Local
- Anthralin
- Juniper Tar
- Pine Tar

Antiemetic
- Prochlorperazine
- Thiethylperazine Maleate
- Trimethobenzamide Hydrochloride
- Trimethobenzamide Hydrochloride and Benzocaine [Suppositories]

Antiflatulent

Antifungal

Antifungal, Local
- Candicidin
- Carbol-Fuchsin Solution
- Resorcinol Ointment, Compound
- Salicylanilide
- Sodium Propionate
- Triacetin
- Undecylenic Acid
- Zinc Undecylenate

Antihistaminic
- Antazoline Phosphate
- Bromodiphenhydramine Hydrochloride
- Brompheniramine Maleate
- Carbinoxamine Maleate
- Chlorcyclizine Hydrochloride
- Chlorothen Citrate
- Chlorpheniramine Maleate [Injection]
- Cyproheptadine Hydrochloride
- Dexbrompheniramine Maleate
- Dexchlorpheniramine Maleate
- Dimethindene Maleate
- Methapyrilene Hydrochloride
- Phenindamine Tartrate
- Pyrilamine Maleate
- Pyrrobutamine Phosphate
- Triprolidine Hydrochloride

Antihypertensive
- Bendroflumethiazide
- Benzthiazide
- Chlorothiazide

Cyclothiazide
Hydralazine Hydrochloride
Hydroflumethiazide
Methyclothiazide
Pargyline Hydrochloride
Polythiazide
Rauwolfia Serpentina
Rescinnamine
Sodium Chlorothiazide [for Injection]
Syrosingopine
Trichlormethiazide
Trimethidinium Methosulfate

Anti-infective, Local

Benzethonium Chloride
Cetylpyridinium Chloride
Fuchsin, Basic
Furazolidone
Furazolidone and Nifuroxime [Powder and Suppositories]
Ichthammol
Iodine [Ampuls and Solution]
Iodochlorhydroxyquin and Hydrocortisone [Powder and Ointment]
Iodoform
Methylbenzethonium Chloride
Neomycin Sulfate, Polymyxin B Sulfate, and Zinc Bacitracin [Ointment]
Nifuroxime
Nitrofurazone
Nitromersol
Povidone-Iodine
Silver Protein, Mild
Sodium Hypochlorite [Solution, Diluted]
Thimerosal
Triclobisonium Chloride

Anti-infective, Local (Dental)

Camphorated Parachlorophenol
Parachlorophenol

Anti-infective, Local (Ophthalmic)

Neomycin Sulfate, Polymyxin B Sulfate and Gramicidin [Ophthalmic Solution]
Yellow Mercuric Oxide

Anti-inflammatory (Non-steroid)

Indomethacin
Oxyphenbutazone

Antileishmanial

Antimalarial

Amodiaquine Hydrochloride
Quinine Dihydrochloride

Antimethemoglobinemic (Cyanide Antidote)

Antinauseant

Antineoplastic

Dromostanolone Propionate
Pipobroman
Thioguanine
Triethylenemelamine
Urethan

Antiperistaltic

Antipolycythemic

Antiprotozoan

Chlortetracycline Hydrochloride

Antipruritic

Cyproheptadine Hydrochloride
Methdilazine
Methdilazine Hydrochloride
Trimeprazine Tartrate

Antipruritic, Local

Antirickettsial

Chloramphenicol [for Suspension, Sterile]

Antiseborrheic

Resorcinol Monoacetate
Selenium Sulfide

Antitrichomonal

Furazolidone
Furazolidone and Nifuroxime [Powder and Suppositories]
Iodochlorhydroxyquin Powder, Compound
Nifuroxime

Antitrypanosomal

Antitussive

Benzonatate
Carbetapentane Citrate
Codeine
Codeine Sulfate
Dextromethorphan Hydrobromide
Levopropoxyphene Napsylate
Noscapine
Terpin Hydrate and Dextromethorphan Hydrobromide [Elixir]

Antiviral

Antiviral (Prophylactic)

Amantadine Hydrochloride

Astringent

Bismuth [Milk]

Astringent, Local

Alum
Aluminum Chloride
White Lotion
Zinc Oxide Paste with Salicylic Acid

Astringent (Ophthalmic)

Blood Neutralizer (Isoagglutinins, Group O Blood)

Blood Group Specific Substances A and B

Blood Replenisher

Blood-volume Supporter

Bone Splint, Internal

Bronchodilator

Oxtriphylline
Theophylline, Ephedrine Hydrochloride, and Phenobarbital [Tablets]

Calcium Supplement

Calcium Lactate

Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic

Carbonic Anhydrase Inhibitor

Cardiac Depressant (Anti-arrhythmic)

Cardiotonic

Acetyldigitoxin
Digitalis [Capsules]
Digitoxin [Injection]
Gitalin
Lanatoside C

Cathartic

Bisacodyl
Cascara [Tablets]
Cascara Sagrada [Extract and Fluidextract]
Castor Oil, Aromatic
Danthron
Glycerin Suppositories
Magnesium Citrate Solution
Magnesium Hydroxide
Mineral Oil [Emulsion]
Phenolphthalein
Plantago Seed
Potassium Sodium Tartrate
Senna
Sodium Carboxymethylcellulose [Tablets]
Sodium Phosphate

Caustic

Chelating Agent (Heavy Metals Antidote)

Chemotic

Ethylmorphine Hydrochloride

Choleretic

Dehydrocholic Acid
Sodium Dehydrocholate [Injection]

Cholinergic

Ambenonium Chloride
Methacholine Bromide
Methacholine Chloride

Cholinergic (Ophthalmic)

Isoflurophate [Ophthalmic Ointment]

Cholinesterase Reactivator (Organophosphate Antidote)

Dental Caries Prophylactic

Stannous Fluoride

Depigmenting agent

Hydroquinone
Monobenzone

Detergent

Green Soap
Green Soap Tincture

Diagnostic Aid

CIRCULATION TIME
Sodium Dehydrocholate [Injection]
GASTRIC SECRETION
Azuresin
PERNICIOUS ANEMIA
Cyanocobalamin Co 60 [Capsules]
RADIOPAQUE-CHOLANGIOGRAPHIC AND CHOLECYSTOGRAPHIC
Calcium Ipodate
RADIOPAQUE-CHOLECYSTOGRAPHIC
Sodium Ipodate
RADIOPAQUE-HYSTEROSALPINGOGRAPHIC
Iodized Oil
RADIOPAQUE-UROGRAPHIC
Iodopyracet [Injection]
Sodium Methiodal

Digestive Aid

Pancreatin
Peppermint [Spirit]

Disinfectant

Cresol
Cresol, Saponated Solution
Sodium Hypochlorite [Solution]

Diuretic

Bendroflumethiazide
Benzthiazide
Chlormerodrin
Chlorothiazide
Cyclothiazide
Hydroflumethiazide
Methyclothiazide
Polythiazide
Sodium Chlorothiazide [for Injection]
Theophylline [Tablets]
Trichlormethiazide

Electrolyte Replenisher

Fructose
Fructose and Sodium Chloride [Injection]
Lactated Potassic Saline [Injection]
Potassium Gluconate
Sodium Chloride and Dextrose [Tablets]

Emetic

Apomorphine Hydrochloride

Estrogen

Benzestrol
Chlorotrianisene
Dienestrol
Diethylstilbestrol Dipropionate
Estradiol
Estradiol Benzoate
Estradiol Cypionate
Estradiol Dipropionate
Estrone
Mestranol [Tablets]

Estrogen-progestin (Ovulation Control)

Chlormadinone Acetate and Mestranol [Tablets]
Ethinyl Estradiol and Dimethisterone [Tablets]

Expectorant

Glyceryl Guaiacolate
Potassium Guaiacolsulfonate
Potassium Iodide [Solution]
Terpin Hydrate
Terpin Hydrate and Codeine [Elixir]
Terpin Hydrate and Dextromethorphan Hydrobromide [Elixir]

Fecal Softener
Dioctyl Calcium Sulfosuccinate

Fluid Replenisher
Fructose
Fructose and Sodium Chloride [Injection]
Lactated Potassic Saline [Injection]

Gas

Glucocorticoid
Betamethasone
Betamethasone Acetate
Betamethasone Sodium Phosphate
Betamethasone Sodium Phosphate and Betamethasone Acetate [Suspension, Sterile]
Betamethasone Valerate
Dexamethasone [Aerosol and Elixir]
Dexamethasone Sodium Phosphate [Cream, Ophthalmic Ointment, and Ophthalmic Solution]
Fluocinolone Acetonide
Fluorometholone
Fluprednisolone
Flurandrenolide
Hydrocortisone [Lotion]
Iodochlorhydroxyquin and Hydrocortisone [Powder and Ointment]
Methylprednisolone
Methylprednisolone Acetate
Methylprednisolone Sodium Succinate
Neomycin Sulfate and Hydrocortisone Acetate [Lotion]
Paramethasone Acetate
Prednisolone Succinate
Prednisolone Sodium Succinate [for Injection]
Triamcinolone Acetonide [Aerosol]
Triamcinolone Diacetate

Gonadotropin

Gout Suppressant

Hemostatic
Aminocaproic Acid

Hemostatic, Local
Thrombin

Hemostatic (Antihemophilic)

Hyperglycemic

Hypoglycemic
Acetohexamide

Hypokalemic

Immunizing agent
Tetanus and Gas Gangrene Antitoxins

Iodide Supplement
Potassium Iodide [Solution]

Iron Supplement
Dextriferron [Injection]
Ferrous Gluconate
Ferrous Sulfate [Syrup]

Irrigation Solution
Ringer's Solution

Irritant, Local
Camphor [Spirit]

Keratolytic
Resorcinol Monoacetate
Resorcinol [Compound Ointment]

Lipotropic
Methionine

Mineralcorticoid
Desoxycorticosterone Acetate [Pellets]
Desoxycorticosterone Pivalate

Multivitamin Supplement
Hexavitamin [Capsules]
Hexavitamin [Tablets]

Mydriatic

Non-nutritive Sweetner
Calcium Cyclamate
Calcium Cyclamate and Calcium Saccharin [Solution and Tablets]
Calcium Saccharin
Sodium Cyclamate
Sodium Cyclamate and Sodium Saccharin [Solution and Tablets]
Sodium Saccharin

Nutrient
Aminoacetic Acid
Fructose
Fructose and Sodium Chloride [Injection]
Sodium Chloride and Dextrose [Tablets]

Oxygen Diluent

Oxytocic

Parasiticide
Sublimed Sulfur

Parathyroid Supplement

Pediculicide

Pharmaceutic Aid
AEROSOL PROPELLANT
Dichlorodifluoromethane
Dichlorotetrafluoroethane
Trichloromonofluoromethane
ALCOHOL DENATURANT
Denatonium Benzoate
Methyl Isobutyl Ketone
Sucrose Octaacetate
AMMONIA, SOURCE OF
Ammonium Carbonate
Amonia Solution, Strong
ANTIOXIDANT
Ascorbyl Palmitate
Hypophosphorous Acid
BACTERIOSTATIC
Benzyl Alcohol
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
BUFFERING AGENT
Boric Acid
Potassium Phosphate, Monobasic
Tartaric Acid

- COLOR
  - Amaranth Solution, Compound
  - Caramel
- DISPERSING AGENT
  - Polyethylene Glycol 300
  - Povidone
- EMOLLIENT
  - Almond Oil
  - Rose Water Ointment
  - Starch Glycerite
- EMULSIFYING AGENT
  - Cetyl Alcohol
  - Glyceryl Monostearate
  - Sodium Stearate
- FLAVOR
  - Benzaldehyde
  - Caraway
  - Caraway Oil
  - Cardamom Seed
  - Cardamom Tincture, Compound
  - Cinnamon
  - Eriodictyon
  - Ethyl Acetate
  - Ethyl Vanillin
  - Eucalyptus Oil
  - Myristica Oil
  - Orange Flower Oil
  - Orange Flower Water
  - Orange Peel, Bitter
  - Peppermint Spirit
  - Pine Needle Oil
  - Spearmint
  - Spearmint Oil
  - Tolu Balsam Tincture
  - Vanilla
- OINTMENT BASE
  - Ointment, Yellow
  - Petrolatum
  - Rose Water Ointment
- PERFUME
  - Almond Oil
  - Lavender Oil
  - Orange Flower Oil
  - Orange Flower Water
  - Pine Needle Oil
  - Rose Oil
  - Rose Water, Stronger
- PRESERVATIVE
  - Phenylethyl Alcohol
  - Potassium Sorbate
  - Sorbic Acid
- SOLVENT
  - Acetic Acid, Diluted
  - Acetone
  - Ammonia Solution, Strong
  - Amylene Hydrate
  - Chloroform
  - Isopropyl Alcohol
  - Phosphoric Acid
  - Polyethylene Glycol 300
- STIFFENING AGENT
  - Cetyl Alcohol
  - Paraffin
  - Rosin
  - Sodium Stearate
  - Yellow Wax
- SUPPOSITORY BASE
- SURFACTANT
  - Monoethanolamine
  - Octoxynol
- SUSPENDING AGENT
  - Hydroxypropyl Methylcellulose
  - Povidone
  - Silicon Dioxide, Colloidal
  - Sodium Alginate
- TABLET BASE
  - Calcium Sulfate
  - Cellulose, Microcrystalline
  - Silicon Dioxide, Colloidal
- TABLET BINDER
  - Ethylcellulose
- TABLET COATING
- TABLET DISINTEGRANT
- TABLET LUBRICANT
  - Calcium Stearate
- VEHICLE
  - Acacia Syrup
  - Benzaldehyde Elixir, Compound
  - Eriodictyon Syrup, Aromatic
  - Iso-Alcoholic Elixir
  - Mineral Oil, Light
  - Orange Flower Water
  - Peppermint Water
  - Persic Oil
  - Polyethylene Glycol 1540
  - Tolu Balsam Syrup

Pigmenting Agent (Photosensitizer)
- Trioxsalen

Posterior Pituitary Hormones (Mixed)
- Posterior Pituitary

Potentiator (Nonspecific)

Progestin
- Chlormadinone Acetate
- Dimethisterone
- Dydrogesterone
- Ethisterone
- Norethindrone [Tablets]
- Norethindrone Acetate
- Progesterone

Protectant
- Pectin

Protectant (Dental)
- Zinc-Eugenol Cement

Protectant, Local
- Peruvian Balsam
- White Lotion
- Zinc Oxide Paste with Salicylic Acid

Protein and Vitamin B-complex, Source of
- Dried Yeast

Proteolytic
- Chymotrypsin
- Trypsin, Crystallized

Relaxant, Skeletal Muscle
- Dimethyl Tubocurarine Iodide
- Methocarbamol
- Orphenadrine Citrate

Relaxant, Smooth Muscle
- Papaverine Hydrochloride
- Theophylline [Tablets]
- Theophylline Sodium Acetate
- Theophylline Sodium Glycinate

Rubefacient

Alcohol, Rubbing
Isopropyl Rubbing Alcohol
Peruvian Balsam
Pine Tar

Scabicide

Benzyl Benzoate [Lotion]
Sublimed Sulfur

Sclerosing Agent

Sedative

Amobarbital [Elixir]
Aprobarbital
Butalbital
Chloral Betaine
Ethchlorvynol
Ethinamate
Glutethimide
Mephobarbital
Methyprylon
Propiomazine Hydrochloride
Sodium Butabarbital
Sodium Secobarbital and Sodium Amobarbital [Capsules]
Sodium Vinbarbital [Injection]
Theophylline, Ephedrine Hydrochloride, and Phenobarbital [Tablets]
Vinbarbital

Spermatocide

Spreading Agent

Hyaluronidase [for Injection]

Stimulant, Central

Amphetamine Sulfate
Citrated Caffeine
Dextroamphetamine Phosphate
Ethamivan
Nikethamide
Pentylenetetrazol
Picrotoxin

Stimulant, Central (Barbiturate Antidote)

Stimulant, Central (Convulsant)

Flurothyl

Stimulant, Respiratory

Ammonia Spirit, Aromatic
Doxapram Hydrochloride
Ethamivan
Nikethamide
Picrotoxin

Sulfide, Source of

Sulfurated Potash

Surgical Aid

Thyroid Suppressant

Methylthiouracil

Thyroid Supplement

Tranquilizer (Major)

Acetophenazine Maleate
Carphenazine Maleate
Chlorprothixene
Diazepam
Fluphenazine Enanthate
Fluphenazine Hydrochloride
Haloperidol
Perphenazine
Prochlorperazine
Promazine Hydrochloride
Thiopropazate Hydrochloride
Trifluoperazine Hydrochloride
Triflupromazine Hydrochloride

Tranquilizer (Minor)

Chlordiazepoxide
Hydroxyzine Hydrochloride
Hydroxyzine Pamoate
Meprobamate [Oral Suspension]
Oxazepam
Tybamate

Uricosuric

Vasodilator

Amyl Nitrite
Erythrityl Tetranitrate, Diluted
Erythrityl Tetranitrate [Tablets]
Pentaerythritol Tetranitrate, Diluted
Pentaerythritol Tetranitrate [Tablets]

Vasodilator, Peripheral

Isoxsuprine Hydrochloride
Nylidrin Hydrochloride

Vasopressor

Angiotensin Amide

Vitamins A and D, Source of

Cod Liver Oil
Nondestearinated Cod Liver Oil
Oleovitamin A and D

Vitamin B-complex, Component of

Niacin

Vitamin B_{12}, Source of

Cobalamin Concentrate

Vitamin E Supplement

Vitamin E

Vitamin K, Form of

Menadiol Sodium Diphosphate [Tablets]
Menadione
Menadione Sodium Bisulfite

General Principles Followed in the Preparation of the National Formulary

The following general principles have been adopted by the National Formulary Board and approved by the Board of Trustees of the American Pharmaceutical Association.

1. Purpose

The basic purpose of the National Formulary shall be the establishment and promulgation of official standards of identity, strength, quality, and purity for drugs admitted thereto.

2. Admissions

The admission of articles to the National Formulary shall be based upon their therapeutic value when intended for use as medicinal agents in man. Other articles may be admitted as pharmaceutic aids or adjuncts which are utilized in pharmaceutical procedures or in the formulation of dosage forms.

Drug combinations may be admitted to the National Formulary if they are therapeutically advantageous and offer a distinct benefit over separate administration of the individual ingredients.

No article shall be admitted to the National Formulary under the proprietary or trademark name, or if the composition is secret. The fact that an article is subject to patent protection shall not constitute any basis for excluding it from admission to the National Formulary (see patent notice, page ii).

A separate monograph shall be provided for each individual substance required as a stated ingredient in a monograph for an NF article, unless such substance is recognized in the concurrent USP.

3. Format

Standards shall be set forth in the form of distinct monographs for the individual drug entities and dosage forms which are approved for admission to the NF. Each monograph generally will include a title, definition, description, and other pertinent specifications. Such specifications may consist of test procedures, limit tests, and assays.

4. Nomenclature

The title of each drug monograph in the National Formulary shall be in English. Only a single monograph title shall be given for each drug; no synonyms or subordinate titles shall be provided. However, in the case of drugs of a definite chemical composition, the systematic chemical name may also be given in the monograph.

The titles of monographs shall be, as far as possible, convenient for prescribing and dispensing and in harmony with general usage.

Short titles wherever needed shall be coined for articles with cumbersome names. Such titles of drugs admitted to the NF shall be in general accord with the names selected by the United States Adopted Names (USAN) Council for those articles. Furthermore, NF monograph titles shall usually be identical to the International Nonproprietary Names (INN) of the World Health Organization (WHO), since it is general USAN Council policy to strive for uniformity between names selected by the Council and those selected by the WHO.

The chemical names of organic compounds shall correspond to the systematic chemical names as employed by *Chemical Abstracts* for index purposes. The structural formulas provided in the monographs for cyclic organic compounds shall be constructed such that the ring systems are portrayed in *Chemical Abstracts* and/or International Union of Pure and Applied Chemistry (IUPAC) orientation.

Botanical and zoological names shall conform to the rules of the International Botanical Congress and the International Zoological Congress, respectively.

5. Compounded Preparations

A specific formula with manufacturing directions may be included in a monograph where it is possible or desirable to compound the preparation on a small scale or without extensive manufacturing equipment.

6. Official Definitions

A statement, known as the official definition, shall be given where possible in each monograph to define the NF article.

Official definitions relating to synthetic organic chemicals or to inorganic chemicals shall include a statement of the composition based upon the established minimum or minimum and maximum percentage of the chemical as determined by an official *Assay* unless other criteria are equally suitable for such determination.

The official definition for drugs of vegetable origin shall indicate, as far as possible, the part or parts of the plant constituting the drug and the botanical name or names of the plant or plants yielding the drug. The official definition for drugs of animal origin shall indicate, as far as possible, the part or parts of the animal from which the drug is derived and the zoological name or names of the animal or animals yielding the drug. The established minimum and maximum percentages of active constituents shall also be stated in definitions for drugs of vegetable or animal origin for which suitable quantitative methods of assay are provided.

In the absence of an *Assay*, or reference to an official *Assay*, or other means of quantitative determination in lieu of an *Assay*, pertaining to an article of known structure, the official definition shall, as a minimum, consist of the chemical name, the molecular formula, and the structural formula of that article, and no tolerance statement of minimum or minimum and maximum percentage shall be given in such cases. National Formulary policy, however, shall be to include a suitable *Assay* in each monograph wherever it is feasible to do so.

Percent concentrations in definitions shall be indicated as (w/v), (v/v), and so forth, in all cases; except where no indication is given, the percent is weight to weight.

Statements regarding permissive ingredients may be included in the definition only where needed for a specific purpose, or where the nature of the article would normally prohibit the addition of other ingredients.

7. Standards for Identity, Strength, Quality, and Purity

In order to ensure drugs of high medicinal and pharmaceutical value, suitable standards of identity, strength, quality, and purity shall be provided in the monographs on drugs in the National Formulary. The specified tolerances and limits shall be based upon such quality characteristics as might be expected to distinguish a product produced from suitable raw materials under recognized conditions and procedures of good manufacturing practice.

In describing the procedures to be followed, reference may be made in any monograph to any official general or specific tests, assays, or processes.

Assay procedures should be directed at measuring the therapeutically active portion of the molecule in monographs for articles such as salts, esters, amides, complexes, or chelates.

Only one method or procedure shall be specified in connection with each individual test prescribed for the determination of the identity, strength, quality, or purity of an NF article; no alternate procedure may be included in such tests.

In spectrophotometric procedures, the use of reference substances shall be specified, and absorptivity values shall be avoided. For these procedures NF Reference Standards shall be specified wherever feasible.

When an ultraviolet or infrared spectrophotometric method is utilized in the *Assay* in a monograph for a dosage form, suitable preliminary steps shall be provided in the *Assay* procedure to permit the separation and isolation of the ingredient being determined, thereby eliminating possible interference from common absorbing substances, prior to performing the spectrophotometric measurement.

Preference shall be given to the use of different types of *Assay* procedures in the respective monographs for the drug entity and its dosage form. Purity or identity tests generally shall be based upon a different analytical method than that forming the basis of the procedure for the *Assay* in the same monograph.

Statements of the distinctive microscopic structural elements in powdered drugs of vegetable or animal origin may be included in the monographs as a means of determining identity, strength, quality, and purity.

8. Packaging and Storage

A statement prescribing the specific type of container in which the article is to be packaged and the conditions of storage, including any necessary precautions such as avoidance of exposure to light, moisture, and extreme temperature, may be included in the monograph for each National Formulary article.

9. Labeling Requirements

A statement may be included in the monograph for any NF article specifying pertinent information which is either required or prohibited in the labeling for that article.

10. Dosage Forms Available

A brief informative statement indicating the amounts of the therapeutically active ingredient usually available in the particular commercially available dosage form may be provided in each dosage form monograph.

11. Category Statements

A brief statement indicating the primary pharmacologic property or therapeutic use of the pertinent article may be included in the monograph for each National Formulary drug. Such statements shall be selected from a systematic, uniform list developed for this specific purpose. The monograph category statement shall generally indicate the basis for recognition of the drug in the NF.

12. Doses

A usual dose for adults may be stated in the monograph on each drug in the National Formulary generally employed internally for medicinal purposes. A usual dosage range may also be provided. These dosage statements are to be interpreted as the amount or amounts which may be expected to produce the intended therapeutic or other effect in the medical condition for which the drug is recognized in the NF. It is to be understood that the NF does not intend that these doses shall be regarded as obligatory by the physician or other duly licensed practitioner, or as forbidding him either to exceed or reduce the doses stated. A declaration to this effect shall be made in the General Notices of the National Formulary.

In certain instances, where deemed advisable, a usual dose for children may be stated.

There shall be appended to the statement of dose of each compound preparation the approximate amount of each therapeutically active ingredient in the usual dose stated.

Preparations for external use should be so indicated and if dilution of a preparation for such use is desirable, the average extent of such dilution may be stated in the monograph.

13. Antibiotics and Biologics

In order to avoid either duplication or conflict of standards, National Formulary monographs generally shall not include test methods, assays, or specifications for antibiotics or biologics which are subject to batch certification or license by government agencies under provisions of federal law. Monographs, in abbreviated form, may appear in the NF for such articles in order to provide official recognition for them, to establish the pertinent monograph title, to indicate their accepted therapeutic value, and to give related general information of interest to pharmaceutical and medical practitioners.

14. NF Reference Standards

Authentic samples of various substances required for use as Reference

Standards in performing National Formulary assays and tests, and for related purposes, may be established where deemed desirable and made available for distribution on order.

15. Atomic Weights

Atomic weights used in the National Formulary shall be in accordance with the latest available report of the International Commission on Atomic Weights.

16. Weights and Measures

The metric system of weights and measures shall be employed in the National Formulary.

17. Solubilities

General solubility statements shall be provided for information only and shall not constitute standards or tests for purity.

18. Standard Temperature

The standard temperature of 25° C. (Celsius) (77° F.) shall be official in the National Formulary except for alcohol percentage statements or other special cases so designated.

19. Powdered Botanical Drugs

Powdered botanical drugs shall be required to represent the entire plant, unless specifically stated otherwise. When the drug can be powdered without residue, this should be required; in other cases, the amount of allowable residue should be stated.

20. Alcohol in Preparations

The permissible range for the content of C_2H_5OH, in percent (v/v), in each National Formulary preparation, where present in readily determinable quantity, shall be stated in the monograph.

21. General Notices

A general notices section just preceding the individual monographs section shall be provided and shall contain references to such matters as pertain in a general way to the interpretation of the text of the National Formulary.

22. General Tests and Reagents

An appropriate section following the individual monographs section shall be included in the National Formulary and shall set forth methods and standards for general tests, processes, techniques, and apparatus that may be referred to in one or more of the individual monographs. In addition, a section relating to special reagents and their specifications, and to special test and volumetric solutions and directions for their preparation and standardization, shall also be provided.

Where deemed desirable, reference may be made to pertinent portions of similar sections appearing in the concurrent United States Pharmacopeia.

Where the National Formulary Board considers it desirable in the interest of drug purity and quality, appropriate chapters may be included in the General Tests section to standardize certain test methods, apparatus, or other procedures even though such methods, apparatus, or procedures may not be specified in any individual National Formulary monographs.

23. General Information

Various subjects of general information to pharmacists, physicians, and others using the National Formulary may be included in a separate section following the sections on general tests and reagents. Information included in this section shall not constitute official standards of identity, strength, quality, or purity.

24. Supplements

When necessary, *Interim Revision Announcements* to the National Formulary may be published in one of the American Pharmaceutical Association periodicals, and reprints made available, upon request, either free or at a nominal charge.

From time to time *Supplements*, incorporating *Interim Revision Announcements* and other additions and corrections, may be printed separately and distributed to registered holders of the current NF who complete and return the request card provided with each copy of the compendium.

GENERAL NOTICES

applying to the standards, tests, and assays of the National Formulary

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The General Notices serve a dual purpose: (a) by providing in summary form the basic guidelines for the interpretation and application of the standards, tests, and assays of the National Formulary; and (b) by obviating the need to repeat continually throughout the book those requirements that are pertinent in numerous instances.

Exceptions to the General Notices occasionally are necessary, in which case the wording in the individual monograph or general test chapter specifically states the directions or the intent. To emphasize that such exceptions do exist, the General Notices employ, where indicated, a qualifying expression such as "unless otherwise specified." Thus, it is understood that the specific wording of standards, tests, and assays is binding wherever deviations from the General Notices exist. By the same token, where no language is given specifically to the contrary, the General Notices apply.

TITLE

The full title of this book, including its supplements, is The National Formulary, Thirteenth Edition. This title may be abbreviated to National Formulary XIII, or to NF XIII. Where the term NF is used, without further qualification, during the period in which this National Formulary is official, it refers to NF XIII.

OFFICIAL

The word "official", as used in this National Formulary or with reference hereto, is synonymous with "National Formulary" and with "pharmacopeial." The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of an official title, and no other names are permissible. Articles bearing the compendial titles are official whether or not the added designation "NF" is used. Articles listed herein are official and the standards set forth in the monographs apply to them only when the articles are intended or labeled for medicinal use and when bought, sold, or dispensed for this purpose.

ATOMIC WEIGHTS AND CHEMICAL FORMULAS

The atomic weights used in computing molecular weights and the factors in the assays and elsewhere are those recommended in 1967 by the International Commission on Atomic Weights.

Chemical formulas, other than those of the definitions, tests, and assays, are given for purposes of information and calculation.

ABBREVIATIONS

The expressions FDA and NIH refer to the Food and Drug Administration and the National Institutes of Health, respectively, both of which are agencies of the federal Department of Health, Education, and Welfare. The expression USP refers to the current edition of the United States Pharmacopeia, USP XVIII, and its supplements. The term Ph.I. refers to the International Pharmacopoeia published as a recommendation on international standards of strength, quality, and purity for drugs by the World Health Organization.

The expressions AOAC, USASI (formerly ASA), and ASTM refer, respectively, to the Association of Official Analytical Chemists, the USA Standards Institute (formerly American Standards Association), and the American Society for Testing and Materials.

The terms C.S. and T.S. refer to Colorimetric Solution and Test Solution, respectively.

TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range are inclusive so that the range consists of the two values themselves and all intermediate values, but no values outside these limits. With the exception of limits in rubric definitions, which are considered significant to the last digit shown, the values of test limits expressed in percentages are considered significant to the next digit; thus, the expression "not less than 9 percent" in a test denotes not less than 9.0 percent, not 8.9 percent. For all other limits expressed numerically, *i.e.*, those not expressed in percentages, the values are considered significant to the last digit shown.

The minimum purity tolerances specified in the definition for National Formulary articles other than dosage forms are established with a view to the use of the articles as drugs. Such limits do not bar the use of articles which more nearly approach 100 percent purity nor do they constitute a basis for a claim that such articles "exceed" the National Formulary quality. Similarly, a dosage form, the active ingredient(s) of which is purported to approach more nearly 100 percent of the labeled amount(s), does not "exceed" the National Formulary requirements by virtue of its having been prepared to closer tolerances than those specified in the monograph.

The tolerances stated in the definition of preparations and dosage forms allow for assay error, for unavoidable variations in compounding, and for deterioration to an extent considered insignificant under practical conditions. The quantity of each ingredient used in preparing the dosage forms shall be equivalent to not less than 100 percent of that called for in the formula or of the amount declared on the label.

The use of the molecular formula for the active ingredient in defining the required strength of a National Formulary article is intended to designate the 100 percent chemical entity.

PERCENTAGE OF ALCOHOL

All alcohol percentage statements refer to percentage, by volume, of C_2H_5OH at 15.56°.

REAGENT STANDARDS

Standards, tests, and assays are provided to govern the quality of the reagents called for in the National Formulary tests and assays. Listing of these reagents, including indicators and solutions employed as reagents, in no way implies that they have therapeutic merit or utility; furthermore, their status as reagents as distinct from official articles is to be clearly indicated in their labeling.

When a test or assay calls for the use of an NF or USP article—other than an NF or USP Reference Standard—as a material standard of reference, a specimen meeting the specifications of the monograph for that article is to be used.

UNITS OF POTENCY

For those antibiotic, pharmacodynamic, and endocrine preparations as well as most of the enzymes, serums, toxins, vaccines, and related products, for which it is still necessary to express the potency in terms of units by reference to a suitable working standard (usually a USP or NF Reference Standard), the individual monographs refer to USP or NF Units of activity. These units are equivalent to the corresponding international units, where such exist, and to the units of activity established by the Food and Drug Administration in the case of antibiotics, and by the National Institutes of Health in the case of biological products.

The potency and dose of some drugs may be defined in terms of mcg. or mg. of the parent drug (*i.e.*, that portion of the molecule which is responsible for the pharmacologic activity), even though the drug may be used in the form of a salt, ester, or some other chemical combination. The full name of the drug is used in labeling.

INGREDIENTS AND PROCESSES

National Formulary dosage forms are prepared from ingredients that meet the requirements of the respective NF or USP monographs for those individual ingredients for which monographs are provided.

Preparations for which a complete composition is given in this National Formulary, unless specifically exempted herein or in the individual monographs, are to contain only the ingredients named in the formulas. However, there may be deviation from the specified processes or methods of compounding, though not from the ingredients or proportions thereof, provided the finished preparation conforms to the relevant standards laid down herein and to preparations produced by following the specified process.

Where a monograph for a preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried prior to use if due allowance is made for the water or other volatile substances present in the quantity taken.

Unless specifically exempted elsewhere in this National Formulary, the identity, strength, quality, and purity of an official article are determined by the definition, description (to the extent that it is applicable, see page 11), physical properties, tests, assays, and other specifications relating to the article, whether incorporated in the monograph itself, in the General Notices, or in the General Tests, Processes, Techniques, and Apparatus section.

Uniformity of Composition

While a demonstration of homogeneity in individual units of a given lot of a National Formulary dosage form may not always be practicable, variations in composition are undesirable and substantial differences in the content of active ingredient between individual capsules, tablets, and other dosage units are to be avoided. (See *Content Uniformity*, page 798.)

Denatured Alcohol

In the manufacture of National Formulary preparations in which alcohol is used only as a solvent and does not remain in the finished product, alcohol especially denatured by the addition of volatile substances, in accordance with federal statutes and regulations of the Internal Revenue Service, may be substituted, but the preparations so made must be identical with those prepared by the processes given in the monographs and must conform to the National Formulary standards set forth.

Added Substances

Unless otherwise specified in the individual monograph, or elsewhere in the General Notices, suitable substances such as bases, carriers, colors, flavors, preservatives, stabilizers, and vehicles may be added to a National Formulary dosage form to enhance its stability, usefulness, or pharmaceutical elegance, or to facilitate its preparation. Such substances may be regarded as suitable only if they are harmless in the amounts used, if they do not exceed a minimum quantity required to provide their intended effect, if their presence does not impair the therapeutic efficacy of the dosage form, and if they do not interfere with the assays and tests prescribed for determining compliance with the National Formulary standards.

Colors—Added substances used solely to impart color may be incorporated in National Formulary articles or preparations, except those intended for parenteral or ophthalmic use. A suitable coloring agent is one that meets the requirements of the Federal Food, Drug, and Cosmetic Act, and that is otherwise appropriate in all respects.

Capsules and Tablets—Capsules and tablets may be manufactured with suitable diluents, colors, lubricants, disintegrants, and adhesives, such as starches, lactose, sucrose, and other innocuous materials. Tablets and the contents of capsules which are intended to be homogeneous are uniform in appearance within a given lot. Substances that are highly adsorbent, *e.g.*, bentonite, are to be avoided in manufacturing tablets of the drugs used in small dosage, such as the cardiac glycosides, alkaloids, and the synthetic estrogens. Tablets may be coated.

Parenteral and Topical Preparations—For the preservation of preparations intended for parenteral administration or topical application, suitable antioxidants and/or antimicrobial preservatives may be added unless interdicted in the monograph. The presence and proportions of added substances, except those for the purpose of adjusting the pH or making the solution isotonic (wherein only the presence and statement of their effect need be stated), are plainly declared on the label of the original container in which the product is sold. The air in the container may be evacuated or be replaced by carbon dioxide, helium, or nitrogen, which fact need not be declared on the label. Surgical sutures may be colored.

Ointments and Suppositories—In official ointments and suppositories, the proportions of the substances constituting the base may be varied to maintain a suitable consistency under different climatic conditions, provided the concentrations of active ingredients are not varied.

TESTS AND ASSAYS

The analytical procedures described in this National Formulary have been designed on the basis that they will be performed by analytical personnel having appropriate training, and that the procedures will be conducted in accord with recognized principles of good analytical practice.

Apparatus

A specification for a definite size or type of container or apparatus in a test or assay is given solely as a recommendation. When volumetric flasks or other exact measuring, weighing, or sorting devices, are specified, this or other equipment of at least equivalent accuracy or calibration must be employed, (for example, see *Volumetric Apparatus*, page 899).

Where an instrument for physical measurement, such as a spectrophotometer, is specified in a test or assay by its distinctive name, another instrument of equivalent or greater sensitivity and accuracy may be used.

Where the use of a centrifuge is specified, the directions are predicated upon the use of apparatus having an effective radius of about 20 cm. (8 inches) and driven at a speed sufficient to clarify the supernatant layer within 15 minutes.

Where tubes or columns are specified, the dimensions refer to internal diameters, unless otherwise specified.

Steam Bath—Where the use of a steam bath is directed, exposure to actively flowing steam or the vapors of vigorously boiling water, or to another form of regulated heat, corresponding in temperature to that of flowing steam, may be used.

Water Bath—Where the use of a water bath is directed without qualification as to temperature, vigorously boiling water is intended.

Foreign Substances

Tests for the presence of foreign substances are provided to limit such substances to amounts that are unobjectionable under conditions in which the medicinal agent is customarily employed.

While one of the primary objects of the National Formulary is to assure the user of official medicinal substances of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity or adulterant that might be present. Tests suitable for detecting impurities, the presence of which is inconsistent with good pharmaceutical practice, may be employed in addition to the tests provided.

Procedures

Assay and test procedures are provided for determining compliance with NF standards of purity and strength. Automated procedures employing the same basic chemistry as those procedures given in the monographs are also recognized as being suitable for determining compliance. Compliance also may be shown by use of alternative methods (including automated procedures), chosen for convenience under special circumstances, provided the results thereby obtained are of equivalent accuracy. However, in the event of doubt or dispute, only the result obtained by the procedure given in this National Formulary is authoritative.

In stating the appropriate quantities to be taken for assays, the use of the word "about" indicates a quantity within 10 percent of the specified amount. However, the quantity taken is accurately determined and the assay result is based upon this exact weight or volume. In performing assay or test procedures, not less than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities of sample weights and volumes than those specified may be taken, provided that such measurement is made with at least equivalent accuracy and that any subsequent steps, such as dilutions, are adjusted accordingly to provide concentrations equivalent to those specified and are made in a manner to provide at least equivalent accuracy.

Where it is directed in the assay of Tablets, to "weigh and finely powder not less than" a given number, usually 20, of the Tablets, it is intended that a counted number of tablets shall be weighed, and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets, and, in turn, is weighed accurately.

Assays and tests, in which it is directed that the substance be previously dried, may be performed on the undried substance and the results calculated on the dried basis, provided a *Loss on drying* test is given in the monograph and that the moisture present will not interfere with the assay or test procedure.

Where the use of a pipet is directed for measuring a sample or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth on page 899, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth on page 899, may be used.

The term "exactly," or expressions such as "25.0 ml." or "25.0 mg.," used with respect to volumetric or gravimetric measurements, indicates that the quantity is to be "accurately measured", or "accurately weighed" within the limits stated under *Volumetric Apparatus*, page 899 or under *Weights and Balances*, page 902.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for spectrophotometric assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession.

Blank Determination—Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test.

Desiccator—The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design which maintains an atmosphere of low moisture content by means of a suitable desiccant in effective condition, such as anhydrous calcium chloride, magnesium perchlorate, phosphorus pentoxide, or silica gel.

Dilution—Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water, or other solvent if specified, in the proportion indicated. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see page 899).

Drying to Constant Weight—The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 500 mcg. per g. of substance taken, the second weighing following an additional hour of drying.

Filter—Unless otherwise indicated the expression "filter" means that the solution should be filtered through filter paper.

Identification Tests—The National Formulary tests headed *Identification* are provided as an aid in verifying the identity of substances taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of a substance taken from a labeled container to meet the requirements of a prescribed identification test indicates that the substance may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the substance under examination.

Ignition to Constant Weight—The specification "ignite to constant weight" means that the ignition shall be continued, at 800 ± 25° unless otherwise indicated, until two consecutive weighings do not differ by more than 500 mcg. per g. of substance taken, the second weighing following an additional 15-minute ignition period.

Indicators—Where the use of a test solution ("T.S.") as an indicator is specified in a test or an assay, 3 drops of the solution shall be added, unless otherwise directed.

Logarithms—Logarithms used in the assays are to the base 10.

Negligible—This term indicates a quantity not exceeding 500 mcg.

Odor—Terms such as "odorless," "practically odorless," "has a faint characteristic odor" or variations thereof in the *Description* apply to examination, after exposure to the air for 15 minutes, of either a freshly opened package of the article, for packages containing not more than 25 g., or, for larger packages, a portion of about 25 g. of the article that has been removed from its package to an open evaporating dish of about 100 ml. capacity. Except in those cases where a specified odor is prohibited, an odor designation is descriptive and is not to be regarded as a standard of quality for a particular lot of an article.

Overnight—The expression "overnight" indicates a time interval of approximately 16 hours.

Pressure Measurements—The term "mm. of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

Solutions—Unless otherwise specified in the individual monograph, all solutions are prepared with *Purified Water*, USP XVIII.

An expression such as "(1 in 10)" means that 1 part *by volume* of a liquid is to be diluted with, or 1 part *by weight* of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts *by volume*.

Where solutions of a specific concentration are specified in an assay, standardized solutions of other normalities or molarities may be used provided allowance is made for the difference in concentration and the error of measurement is not increased thereby.

Specific Gravity—Unless otherwise stated, the specific gravity basis is 25°/25°, *i.e.*, the ratio of the weight of a substance in air at 25° to the weight of an equal volume of water at the same temperature.

Temperatures—Unless otherwise specified, all temperatures in this National Formulary are expressed in centigrade (Celsius) degrees. All measurements are made at 25° unless otherwise directed.

With respect to sterilization processes involving the use of steam under pressure, the stated temperatures are those at the exhaust line of the autoclave when the steam has completely replaced the air.

Time Limit—In conducting the limit tests for impurities (chloride, iron, etc.), 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum—The term "in vacuum" specifies exposure to a pressure of less than 20 mm. of mercury, unless otherwise indicated.

Water—Where water is called for in tests and assays, *Purified Water*, USP XVIII, is to be used. "Carbon dioxide-free water" is purified water that has been boiled vigorously for 5 minutes or more and allowed to cool while protected from absorption of carbon dioxide from the atmosphere.

Water and Loss on Drying—If the water of hydration or adsorbed water of a National Formulary article is determined by the titrimetric method, the test is usually provided under the heading of *Water*. If the determination is made by drying under specified conditions then the test is provided under the heading of *Loss on Drying*. The latter procedure is particularly specified for an article where it is desired to determine all volatile constituents including organic solvents, etc., as well as water.

Description

The *Description* in a monograph is intended to be relatively general in nature. The information embodied therein is usually provided simply to indicate the properties of an article complying with the monograph standards. Statements of chemical and physical attributes that are not definable within reasonably narrow limits—or are not intended to be so defined—are generally included in the *Description* rather than elsewhere in the monograph.

Solubility

The statements concerning solubilities given under the heading *Solubility* in the National Formulary monographs are not standards or tests for purity, but are provided primarily as information for those who use, prepare, and dispense drugs. Only when a special quantitative solubility test is given, and is designated as such, is it a test for purity.

Except as indicated above, the solubility of a National Formulary article in the given solvent is considered to be of minor importance as a means of identification or determination of purity; for these purposes dependence is placed upon the other tests provided in the monographs.

Approximate solubilities of National Formulary substances are indicated by the following descriptive terms:

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	More than 10,000

Soluble National Formulary articles, when brought into solution, may show slight physical impurities, such as fragments of filter paper, fibers, and dust particles, unless excluded by definite tests or other specifications in the individual monographs.

CATEGORIES AND DOSES

Category

A statement of Category usually is provided in each monograph as useful information. It indicates the therapeutic or pharmaceutic basis for recognition in the National Formulary and generally represents an application of the best known pharmacologic action of the article or of its active ingredient. The Category statement pertains to the administration of the drug systemically unless otherwise specified, or if the nature of the drug is such that it is obviously for nonsystemic use. The statement is not intended to limit in any way the choice or use of the article nor to indicate that it has no other activity or utility.

Usual Dose

The Usual Dose generally given in the monograph is that which may be expected ordinarily to produce in adults, following administration in the manner indicated at such time intervals as may be specified, the diagnostic, therapeutic, prophylactic, or other use for which the article is recognized. Administration is by the oral route unless otherwise specified. The Usual Dose is intended to serve only as a guide to the medical practitioner, who may vary it in the best interests of the patient's welfare and in accordance with the variables which affect the action of the drug.

The statements of dosage in the case of Capsules and Tablets are in terms of the content of active ingredient and seldom represent the total weight of the capsule contents or of the tablets.

In some instances, the dosage may be stated in terms of the pharmacologically active portion of the molecule in order to correlate for the information of the practitioner the weight equivalent to salts, esters, or other chemical forms of the same drug moiety.

Usual Dose Range

The Usual Dose Range is intended primarily to guide the pharmaceutical practitioner with respect to seeking confirmation of prescription orders. The time schedule and route of administration where given for the Usual Dose apply also to the Usual Dose Range, unless otherwise specified.

Dose Equivalents

All doses are expressed in the metric system. "Approximate" equivalents in the apothecary system may be obtained from the "Table of Metric Doses with Approximate Apothecary Equivalents." In labeling dosage forms in both the metric and apothecary systems, the approximate equivalent of the exact quantity is enclosed in parentheses.

When prepared dosage forms such as tablets, capsules, etc., are prescribed in the metric system, the corresponding "approximate" apothecary equivalent may be dispensed, and vice versa.

For converting specific quantities in a prescription order which requires compounding, or in converting a pharmaceutical formula from one system of weights or measures to the other, "exact" equivalents must be used (see *Equivalents of Weights and Measures*, page 965).

Sizes Available

The statement on sizes usually available of a dosage form given in the individual monograph is intended solely as information to medical practitioners, pharmaceutical practitioners, and others concerned with the manner in which dosage forms are commonly supplied. The statement on sizes usually available is not intended to bar the manufacture of the article in strengths differing from those listed, or to preclude its being packaged in different volumes, weights, or counts. Unless otherwise stated, the specifications provided in the monograph apply equally to articles packaged in sizes or strengths other than those listed.

PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers

The *container* is the device which holds the drug and which is or may be in direct contact with the drug. The *immediate container* is that which is in direct contact with the drug at all times. The *closure* is a part of the container.

Prior to its being filled, the container should be clean and dry. Special precautions and cleaning procedures may be necessary to ensure that extraneous particulate matter is not introduced into the dosage preparation. The container does not interact physically or chemically with the article placed in it so as to alter significantly the strength, quality, purity, safety, or effectiveness of the drug beyond the official requirements.

The National Formulary requirements for the use of specified containers apply to products when dispensed by the pharmacist unless otherwise indicated in the individual monograph.

Light-Resistant Container, page 795—A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. If light protection is required, a clear and colorless or a translucent container may be made light-resistant by means of an opaque enclosure in which case the label of the container bears a statement that the opaque covering is needed until the contents have been used.

Well-Closed Container—A well-closed container protects the contents from extraneous solids and from loss of the drug under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container—A tight container protects the contents from contamination by extraneous liquids, solids or vapors, from loss of the drug, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight re-closure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of a drug.

A gas cylinder is a metallic tight container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, ethylene, helium, nitrous oxide, and oxygen, the Pin-Index Safety System of matched fittings, is recommended for cylinders of Size E or smaller.

Hermetic Container—A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-Dose Container—A single-dose container is a hermetic container holding a quantity of sterile drug intended for parenteral administration as a single dose, and which when opened cannot be re-sealed with assurance that sterility has been maintained.

Note—A single-dose container should not be confused with a "unit-dose container," which constitutes a single dose for a product which is generally not intended for parenteral administration.

Multiple-Dose Container—A multiple-dose container is a hermetic container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Storage Temperature

Specific directions are stated in certain monographs with respect to the temperature at which NF articles should be stored where it is considered that storage at lower or higher temperatures may produce undesirable results. The conditions are defined by these terms:

Cold—Any temperature not exceeding 8° (46° F.). A *refrigerator* is a cold place in which the temperature is maintained thermostatically between 2° and 8° (36° and 46° F.).

Cool—Any temperature between 8° and 15° (46° and 59° F.). An article for which storage in a cool place is indicated may also be stored in a refrigerator unless otherwise specified in the monograph.

Room Temperature—The temperature prevailing in a working area. *Controlled Room Temperature* is maintained thermostatically between 15° and 30° (59° and 86° F.).

Excessive Heat—The expression "excessive heat" designates temperatures above 40° (104° F.).

Protection from Freezing—Where, in addition to the risk of breakage of the original container, freezing subjects a product to loss of strength of potency or to destructive alteration of the dosage form, the container label bears appropriate notice to protect the product from freezing.

Storage in Bulk and Under Nonspecific Conditions

Bulk packages are exempt from the storage requirements when the products are intended for manufacture or for subsequent re-packaging for the dispenser or ultimate distributor. Where no specific storage directions or limitations are provided, it is to be understood that the storage conditions include protection from moisture, freezing, and excessive heat. Such storage areas shall include facilities which are clean and subject to appropriate sanitation and maintenance.

Labeling

Articles in this National Formulary are subject to compliance with such labeling requirements as may be promulgated by federal regulations in addition to the NF requirements set forth for the articles (see notice, page ii).

A shipping container, unless such container is also essentially the immediate container or the outside of the consumer package, is exempt from the labeling requirements of this National Formulary.

Labeling Vitamin-Containing Products—The vitamin content of National Formulary preparations shall be stated on the label in metric units. The amounts of vitamins A and D may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of vitamin A alcohol (retinol).

Amount of Ingredient per Dosage Unit—National Formulary articles in tablet, capsule, or other unit dosage form, shall be labeled to express the quantity of each therapeutically active ingredient contained in each such unit. National Formulary articles not in unit dosage form shall be labeled to express the quantity of each therapeutically active ingredient in 1 ml. or in 1 g., except that oral liquids may, alternatively, be labeled in terms of 5 ml.

Special Tablets—The label of any form of tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used. Where a tablet is enteric-coated, the label so states.

Expiration Date—The monographs for several National Formulary articles, particularly those which are biologic in origin, require that the label bear an expiration date, which is determined conservatively as the date beyond which the article might not have the required potency, provided the article is stored under the prescribed storage conditions.

VEGETABLE AND ANIMAL DRUGS

The requirements for vegetable and animal drugs apply to the articles as they enter commerce; however, batches of such drugs intended solely for the manufacture or isolation of volatile oils, alkaloids, glycosides, or other active principles may depart from such requirements.

Foreign Matter

Vegetable and animal drugs are to be as free as reasonably practicable from microorganisms, insects, and other animal contamination, including animal excreta. Furthermore, they shall be free from pathogenic organisms. They shall show no abnormal discoloration, abnormal odor, sliminess, or other evidence of deterioration.

The amount of foreign inorganic matter in vegetable or animal drugs, estimated as *Acid-insoluble ash*, shall not exceed 2 percent of the weight of the drug, unless otherwise specified in the individual monograph.

Before vegetable drugs are ground or powdered, stones, dust, lumps of soil, and other foreign inorganic matter are removed by mechanical means.

In commerce it is seldom possible to obtain vegetable drugs in a state of absolute purity, and some adherent or admixed, innocuous, foreign matter usually is not detrimental. No poisonous, dangerous, or otherwise noxious foreign substance, however, may be present. Foreign organic matter includes any part of the plant not specified as constituting the drug.

Preservation

Vegetable or animal substances may be protected from insect infestation by means of a suitable fumigant, such as chloroform, carbon tetrachloride, or methyl bromide.

WEIGHTS AND MEASURES

Metric Units

The metric system of weights and measures is used in this National Formulary. The units and the abbreviations commonly employed are as follows:

m. = meter
cm. = centimeter
mm. = millimeter
μ = micron (0.001 mm.)
mμ = millimicron
kg. = kilogram
g. = gram
mg. = milligram
mcg. = microgram[*]
l. = liter
ml. = milliliter[†]
μl. = microliter

Percentage Solutions

Percentage concentrations of solutions are expressed as follows:

Percent Weight in Weight (w/w)—expresses the number of g. of a constituent in 100 g. of solution.

Percent Weight in Volume (w/v)—expresses the number of g. of a constituent in 100 ml. of solution, and is used regardless of whether water or another liquid is the solvent.

Percent Volume in Volume (v/v)—expresses the number of ml. of a constituent in 100 ml. of solution.

The term *percent*, as used in this National Formulary, without qualification means, for mixtures of solids, percent weight in weight; for solutions or suspensions of solids in liquids, percent weight in volume; for solutions of liquids in liquids, percent volume in volume; for mixtures of liquids in solids, percent volume in weight (*e.g.*, ointments); and for solutions of gases in liquids, percent weight in volume. For example, a 1 percent solution is prepared by dissolving 1 g. of a solid or 1 ml. of a liquid in sufficient of the solvent to make 100 ml. of the solution.

In dispensing prescription medications, slight changes in volume owing to variations in room temperatures may be disregarded.

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[*] The abbreviation "mcg." has come into general use in pharmaceutical literature and labeling. The term "gamma," symbolized by γ, is customarily used for microgram in biochemical literature, while "μg" is generally accepted as the abbreviation in the literature of physics and physical chemistry.

[†] One milliliter (ml.) is used herein as the equivalent of 1 cubic centimeter (cc.).

MONOGRAPHS
on drugs, chemicals, and preparations

Acacia Syrup

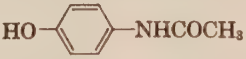
Acacia, granular or powdered	**100 g.**
Sodium Benzoate	**1 g.**
Vanilla Tincture	**5 ml.**
Sucrose	**800 g.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Mix the acacia, sodium benzoate, and sucrose; then add 425 ml. of purified water, and mix well. Heat the mixture on a steam bath until solution is completed. When cool, remove the scum, add the vanilla tincture and sufficient purified water to make the product measure 1000 ml., and strain if necessary.

Packaging and storage—Preserve Acacia Syrup in tight containers, and avoid excessive heat.

CATEGORY—Vehicle.

Acetaminophen



4′-Hydroxyacetanilide

$C_8H_9NO_2$ Mol. wt. 151.17

Acetaminophen contains not less than 98.0 percent and not more than 100.5 percent of $C_8H_9NO_2$, calculated on the anhydrous basis.

Description—Acetaminophen occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

Solubility—Acetaminophen is soluble in boiling water and in sodium hydroxide T.S. It is freely soluble in alcohol.

Identification—To 10 ml. of a solution of Acetaminophen (1 in 100) add 1 drop of ferric chloride T.S.: a violet-blue color is produced.

Melting range, page 814—Acetaminophen melts between 168° and 172°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Acetaminophen, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Acetaminophen Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Acetaminophen in 0.1 *N* hydrochloric acid in methanol (1 in 100) exhibits maxima and minima at the same wavelengths as that of NF Acetaminophen Reference Standard, similarly measured.

pH, page 824—The pH of a saturated solution of Acetaminophen is between 5.3 and 6.5.

Water, page 900—Determine the water content of Acetaminophen by the titrimetric method; not more than 0.5 percent is found.

Residue on ignition, page 858—Acetaminophen yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—Shake 1 g. of Acetaminophen with 25 ml. of water, filter, and add 1 ml. of diluted nitric acid: the acidified filtrate shows no more chloride than corresponds to 0.2 ml. of 0.02 *N* hydrochloric acid (0.014 percent).

Sulfate, page 784—Shake 1 g. of Acetaminophen with 25 ml. of water, filter, and add 2 ml. of diluted acetic acid followed by 2 ml. of barium chloride T.S.: the mixture shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (0.02 percent).

Sulfide—Place about 2.5 g. of Acetaminophen in a 50-ml. beaker. Add 5 ml. of ethyl alcohol and 1 ml. of diluted hydrochloric acid. Moisten a piece of lead acetate test paper with water and fix to the underside of a watch glass. Cover the beaker with the watch glass so part of the lead acetate paper hangs down near the pouring spout of the beaker. Heat the contents of the beaker just to boiling on a hot plate: no coloration or spotting of the test paper occurs.

Heavy metals, *Method II*, page 806—The heavy metals limit for Acetaminophen is 10 parts per million.

Readily carbonizable substances, page 856—Dissolve 500 mg. of Acetaminophen in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid A.

Free *p*-aminophenol—Dissolve 8 mg. of sodium acetate in 50 ml. of water, and prepare a slurry of this solution with 20 g. of silica gel HR containing colloidal silicon dioxide as a binder. From this slurry, prepare a chromatographic plate (see page 789) having a 0.5-mm. layer of the silica gel. To the plate apply 50 μl. of a solution of Acetaminophen in alcohol containing 200 mg. per ml., and 50 μl. of a standard solution of *p*-aminophenol in alcohol containing 50 mg. per ml. Allow the spots to dry, and develop the chromatogram in an unsaturated chamber in a solvent system consisting of methyl ethyl ketone and acetic acid (9:1) until the solvent front has moved at least 15-cm. from the origin. Remove the plate from the developing chamber, and allow the solvent to evaporate. Spray the plate with a 1 in 1000 solution of *p*-dimethylaminocinnamaldehyde in alcohol containing 1 percent hydrochloric acid, and locate the spots by visual inspection after 2 minutes: any red spot produced by the sample, at an R_f value of about 0.25, is no greater in size or intensity than the red spot produced by the standard at the same R_f value, corresponding to not more than 0.25 percent of free *p*-aminophenol.

***p*-Chloroacetanilide**—Transfer 1.0 g. of Acetaminophen to a 15-ml. glass-stoppered centrifuge tube, add 5.0 ml. of ether, shake mechanically for 30 minutes, and centrifuge at 1000 r.p.m. for 15 minutes or until a clean separation is obtained. Apply 100 μl. of the supernatant liquid to a chromatographic plate, prepared as directed under *Free p-aminophenol*, and apply 20 μl. of a standard solution in alcohol containing 10 mcg. of *p*-chloroacetanilide per ml. to the same plate. Allow the spots to dry, and develop the chromatogram in an unsaturated chamber in a solvent system consisting of chloroform-benzene-acetone (65:10:25) until the solvent front has moved at least 12 cm. from the origin. Remove the plate from the developing chamber, and allow the solvent to evaporate. Irradiate the plate under shortwave ultraviolet light at a distance of about 4 cm. above the plate for 10 minutes, and without delay locate the spots by visual inspection under longwave ultraviolet light: any light blue fluorescent spot produced by the sample, at an R_f value of about 0.5–0.6, is no greater in size or intensity than that produced by the standard at the same R_f value, corresponding to not more than 10 parts per million of *p*-chloroacetanilide.

Assay—Transfer to a 250-ml. volumetric flask about 125 mg. of Acetaminophen, accurately weighed, add methanol to volume, and mix. Transfer 5.0 ml. of this solution to a 500-ml. volumetric flask, add 5 ml. of 0.1 *N* hydrochloric acid, and dilute to volume with methanol. Concomitantly determine the absorbance of this solution and of a solution of NF Acetaminophen Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml. in 1-cm. cells, at the maximum at about 249 mμ, with a suitable spectrophotometer, using methanol containing 1 ml. of 0.1 *N* hydrochloric acid per 100 ml. as the blank. Calculate the quantity, in mg., of $C_8H_9NO_2$ in the Acetaminophen taken, by the formula $25C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Acetaminophen in tight, light-resistant containers.

CATEGORY—Analgesic.

USUAL DOSE—**650 mg.** every 4 hours.

USUAL DOSE RANGE—**325 mg. to 650 mg.** Not to exceed **2.6 g.** per 24-hour period.

Acetaminophen Elixir

Acetaminophen Elixir contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_9NO_2$.

Identification—The solution prepared for measurement of absorbance in the *Assay* exhibits a maximum at 249 ± 2 mμ.

pH, page 824—The pH of Acetaminophen Elixir is between 3.8 and 6.1.

Assay—

Standard preparation—Transfer about 80 mg. of NF Acetaminophen Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 10.0 ml. of this last solution to a

100-ml. volumetric flask, add 1 ml. of 0.1 *N* hydrochloric acid, dilute to volume with methanol, and mix.

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 250-mm. tube to which is fused a 5-cm. length of 7-mm. tubing) with the aid of a tamping rod about 45 cm. in length and having a disk with a diameter about 1-mm. less than that of the tube. To 2 g. of purified siliceous earth in a 100-ml. beaker, add 2.0 ml. of a solution containing 1.0 g. of sodium bicarbonate and 4.5 g. of sodium carbonate in each 100 ml., and mix until a fluffy mixture is obtained. Transfer the mixture to the chromatographic tube, and tamp gently to compress the material to a uniform mass.

Assay preparation—Transfer an accurately measured volume of Acetaminophen Elixir, equivalent to about 240 to 250 mg. of acetaminophen, to a 250-ml. volumetric flask, add 2 ml. of sodium hydroxide T.S., dilute to volume with water, and mix. Transfer 2.0 ml. of this solution to a 100-ml. beaker, add 1 drop of hydrochloric acid, swirl to mix, and then add 3.0 g. of purified siliceous earth. Mix thoroughly, and transfer to the chromatographic column. Scrub the beaker with 1 g. of purified siliceous earth mixed with 2 drops of water, transfer the washings to the column, and tamp gently. Place a pledget of fine glass wool on top of the column. Wash the column with 100 ml. of water-saturated chloroform, and discard the eluate. Elute the acetaminophen with 150 ml. of water-saturated ether, collecting the eluate in a 400-ml. beaker. Evaporate the ether to dryness on a steam bath with the aid of a current of air, dissolve the residue in a solvent mixture consisting of 1 ml. of 0.1 *N* hydrochloric acid per 100 ml. of methanol, and quantitatively transfer to a 50-ml. volumetric flask. Rinse the beaker with the solvent mixture, adding the rinsings to the flask, dilute to volume with the solvent mixture, and mix. Transfer 10.0 ml. of this solution to a second 50-ml. volumetric flask, dilute to volume with the solvent mixture, and mix.

Procedure—Concomitantly determine the absorbance of the solutions in 1-cm. cells, at the maximum at about 249 mμ, with a suitable spectrophotometer, using a solvent mixture consisting of 1 ml. of 0.1 *N* hydrochloric acid per 100 ml. of methanol as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_8H_9NO_2$ in each ml. of the Elixir taken by the formula $31.25 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Elixir taken.

Alcohol content, page 772—Determine the alcohol content by the gas-liquid chromatographic procedure, using acetone as the internal standard: Acetaminophen Elixir contains from 6.5 to 10.5 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Acetaminophen Elixir in tight containers and avoid continuous excessive cold.

Elixirs available—Acetaminophen Elixir usually available contains the following amounts of acetaminophen: 100 mg. in 1 ml. and 120 mg. in 5 ml.

CATEGORY and DOSE—See Acetaminophen.

Acetaminophen Tablets

Acetaminophen Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_9NO_2$.

Identification—Triturate an amount of powdered Acetaminophen Tablets, equivalent to about 1 g. of acetaminophen, with 30 ml. of warm alcohol, cool, and filter. Dilute 3 ml. of the filtrate with 10 ml. of water and add 1 drop of ferric chloride T.S.: a violet-blue color is produced.

Disintegration, page 878—The disintegration time limit for Acetaminophen Tablets is 30 minutes.

Weight variation, page 901—Acetaminophen Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Acetaminophen Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 125 mg. of acetaminophen, to a separator, add 10 ml. of water, and shake well. Completely extract with successive portions of a mixture of chloroform and alcohol (3:1). Filter the extracts through a pledget of cotton into a beaker and wash the filter with several small portions of the mixed solvent. Evaporate the combined filtrate and washings on a steam bath with the aid of a current of air. Transfer the residue, with the aid of methanol, to a 250-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 5.0 ml. of the solution to a 500-ml. volumetric flask, add 5 ml. of 0.1 *N* hydrochloric acid, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Acetaminophen Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml. in 1-cm. cells, at the maximum at about 249 mμ, with a suitable spectrophotometer, using methanol containing 1 ml. of 0.1 *N* hydrochloric acid per 100 ml. as the blank. Calculate the quantity, in mg., of $C_8H_9NO_2$ in the portion of the Tablets taken, by the formula $25C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Acetaminophen Tablets in tight, light-resistant containers.

Tablets available—Acetaminophen Tablets usually available contain the following amount of acetaminophen: 325 mg.

CATEGORY and DOSE—See Acetaminophen.

Acetate, Potassium, page 570
Acetate, Sodium, page 635

Diluted Acetic Acid

Diluted Acetic Acid is a solution containing, in each 100 ml., not less than 5.7 g. and not more than 6.3 g. of $C_2H_4O_2$.

Diluted Acetic Acid may be prepared as follows.

Acetic Acid	**158 ml.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Mix the ingredients.

Description—Diluted Acetic Acid is a clear, colorless liquid having a characteristic odor and a sharply acid taste. Its specific gravity is about 1.008.

Solubility—Diluted Acetic Acid is miscible with water, with alcohol, and with glycerin.

Identification—Diluted Acetic Acid responds to the tests for *Acetate,* page 807.

Nonvolatile residue—Evaporate 20 ml. of Diluted Acetic Acid in a tared porcelain dish on a steam bath, and dry at 105° for 1 hour: the weight of the residue does not exceed 1 mg. (50 parts per million).

Chloride—Add 5 drops of silver nitrate T.S. to 10 ml. of a solution of Diluted Acetic Acid (6 in 10): no opalescence is produced.

Sulfate—Add 5 drops of barium chloride T.S. to 10 ml. of a solution of Diluted Acetic Acid (6 in 10): no turbidity is produced.

Heavy metals, page 806—Evaporate 5 ml. of Diluted Acetic Acid to dryness in a porcelain dish on a steam bath. Warm the residue with 2 ml. of diluted acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Diluted Acetic Acid is 10 parts per million.

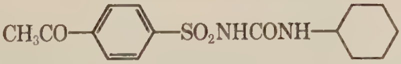
Readily oxidizable substances—To 20 ml. of Diluted Acetic Acid in a glass-stoppered flask, add 0.3 ml. of 0.1 *N* potassium permanganate: the pink color is not changed to brown at once, and the liquid does not become entirely brown or free from a pink tint in less than 30 seconds.

Assay—Transfer 25.0 ml. of Diluted Acetic Acid to a flask, and add 15 ml. of carbon dioxide-free water. Add 3 drops of phenolphthalein T.S., and titrate with 1 *N* sodium hydroxide. Each ml. of 1 *N* sodium hydroxide is equivalent to 60.05 mg. of $C_2H_4O_2$.

Packaging and storage—Preserve Diluted Acetic Acid in tight containers.

CATEGORY—Solvent.

Acetohexamide



1-[(*p*-Acetylphenyl)sulfonyl]-3-cyclohexylurea

$C_{15}H_{20}N_2O_4S$ Mol. wt. 324.40

Acetohexamide contains not less than 97.0 percent and not more than 101.0 percent of $C_{15}H_{20}N_2O_4S$, calculated on the dried basis.

Description—Acetohexamide occurs as a white, crystalline powder. It is practically odorless.

Solubility—Acetohexamide is practically insoluble in water and in ether, and slightly soluble in alcohol and in chloroform. It is soluble in pyridine and in dilute solutions of alkali hydroxides.

Identification—Dissolve about 100 mg. of 2,4-dinitrophenylhydrazine in 1 ml. of sulfuric acid, and cautiously add 5 ml. of alcohol. Cool, filter if necessary to obtain a clear solution, add 5 ml. of a solution of Acetohexamide in hot alcohol (1 in 200), and warm on a steam bath: an orange-yellow precipitate forms.

Melting range, *Class Ia,* page 814—Acetohexamide melts between 184° and 189°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Acetohexamide exhibits maxima only at the same wavelengths as that of NF Acetohexamide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Acetohexamide in 0.01 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Acetohexamide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 247 mμ, do not differ by more than 3 percent.

X-ray diffraction, page 902—The X-ray diffraction pattern of Acetohexamide conforms to the following pattern:

d	I/I_1
16.05	20
9.60	100
7.89	5
5.90	1
5.35	100
4.98	60
4.79	40
4.57	40
4.31	30
4.16	30b
3.92	20
3.75	10
3.63	50
3.50	10
3.28	50
3.15	5
3.07	10
2.91	30
2.75	5
2.63	2
2.57	2
2.50	10
2.40	8
2.36	8
2.30	5
2.18	8
2.08	4
2.04	8
1.96	8
1.72	1
1.62	1

Loss on drying, page 814—Dry Acetohexamide at 105° for 3 hours: it loses not more than 1 percent of its weight.

Selenium—A *Test Preparation* prepared with 100 mg. of Acetohexamide and 100 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Residue on ignition, page 858—Acetohexamide yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Acetohexamide is 20 parts per million.

Assay—Dissolve about 300 mg. of Acetohexamide, accurately weighed, in 40 ml. of dimethylformamide, add 5 drops of thymol blue T.S., and titrate using a magnetic stirrer with 0.1 *N* sodium methoxide to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium methoxide is equivalent to 32.44 mg. of $C_{15}H_{20}N_2O_4S$.

Packaging and storage—Preserve Acetohexamide in well-closed containers.

CATEGORY—Hypoglycemic.

USUAL DOSE—**250 mg.** to **1.0 g.** daily.

USUAL DOSE RANGE—**250 mg.** to **1.5 g.** daily.

Acetohexamide Tablets

Acetohexamide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{20}N_2O_4S$.

Identification—The solution prepared for measurement of absorbance in the *Assay* exhibits a maximum at 249 ± 2 mμ.

Dissolution, *Method I,* page 802—Not less than 15 percent of the labeled amount of $C_{15}H_{20}N_2O_4S$ in Acetohexamide Tablets dissolves into solution within 20 minutes, not less than 30 percent dissolves within 40 minutes, and not less than 50 percent dissolves within 60 minutes, using a stirring speed of 100 r.p.m. and pH 7.6 standard buffer solution as the *Dissolution Fluid.*

Determine the amount of $C_{15}H_{20}N_2O_4S$ in solution by determining the ultraviolet absorption of aliquots removed from the dissolution solution, at 245 mμ, in 1-cm. cells, with a suitable spectrophotometer, using pH 7.6 standard buffer solution as the blank and utilizing a standard curve, representing absorbance *versus* concentration of NF Acetohexamide Reference Standard.

Weight variation, page 901—Acetohexamide Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Acetohexamide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg. of acetohexamide, to a 100-ml. volumetric flask, add 60 ml. of 0.1 *N* sodium hydroxide, and shake for 30 minutes. Dilute to volume with water, mix, and filter, discarding the first 20-ml. of the filtrate. Transfer 20.0 ml. of the subsequent filtrate to a 125-ml. separator, add 2 ml. of diluted hydrochloric acid, and extract with four 40-ml. portions of chloroform, filtering each portion through chloroform-washed paper into a 200-ml. volumetric flask. Dilute to volume with chloroform, and mix. Transfer 20.0 ml. of this solution to a suitable beaker, and evaporate to dryness on a steam bath. Transfer the residue quantitatively, with the aid of 0.1 *N* sodium hydroxide, into a 100-ml. volumetric flask, add 0.1 *N* sodium hydroxide to volume, and mix. Transfer 10.0 ml. of this solution to a third 100-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Acetohexamide Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 249 mμ, with a suitable spectrophotometer, using 0.01 *N* sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_{15}H_{20}N_2O_4S$ in the portion of the Tablets taken by the formula $50C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Acetohexamide Tablets in well-closed containers.

Tablets available—Acetohexamide Tablets usually available contain the following amounts of acetohexamide: 250 and 500 mg.

CATEGORY and DOSE—See Acetohexamide.

Acetone

CH_3COCH_3

2-Propanone

C_3H_6O Mol. wt. 58.08

Acetone contains not less than 99.0 percent of C_3H_6O.

Caution: Acetone is very flammable. Do not use where it may be ignited.

Description—Acetone is a transparent, colorless, mobile, volatile liquid, having a characteristic odor. A solution of Acetone (1 in 2) is neutral to litmus.

Solubility—Acetone is miscible with water, with alcohol, with ether, with chloroform, and with most volatile oils.

Identification—

A: Add 1 ml. of sodium hydroxide T.S. to 1 ml. of a solution of Acetone (1 in 200), warm the mixture, and add a few ml. of iodine T.S.: a yellow precipitate of iodoform appears immediately.

B: Mix 1 ml. of a solution of Acetone (1 in 200) with 5 drops of sodium nitroferricyanide T.S. and 2 ml. of sodium hydroxide T.S., and add a slight excess of acetic acid: a deep red color is produced which develops a bluish purple tint when the mixture is diluted with several volumes of water.

Specific gravity, page 866—The specific gravity of Acetone is not more than 0.789, indicating not less than 99.0 percent of C_3H_6O.

Distilling range, page 782—Acetone distils between 55.5° and 57°.

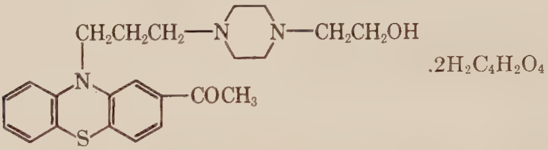
Nonvolatile residue—Evaporate 50 ml. of Acetone in a tared porcelain dish on a steam bath, and dry at 105° for 1 hour: the weight of the residue does not exceed 2 mg. (40 parts per million).

Readily oxidizable substances—Mix 20 ml. of Acetone with 0.1 ml. of 0.1 *N* potassium permanganate in a glass-stoppered bottle: the permanganate color of the mixture does not wholly disappear within 15 minutes.

Packaging and storage—Preserve Acetone in tight containers, remote from fire.

CATEGORY—Solvent.

Acetophenazine Maleate*



10-[3-[4-(2-Hydroxyethyl)-1-piperazinyl]propyl]phenothiazin-2-yl Methyl Ketone Maleate (1:2)

$C_{23}H_{29}N_3O_2S\,.\,2C_4H_4O_4$ Mol. wt. 643.72

Acetophenazine Maleate, dried at 65° for 4 hours, contains not less than 97.0 percent and not more than 103.0 percent of $C_{23}H_{29}N_3O_2S\,.\,2C_4H_4O_4$.

Description—Acetophenazine Maleate occurs as a fine, yellow powder. It melts between 165° and 175° with decomposition.

Solubility—Acetophenazine Maleate is soluble in water. It is slightly soluble in acetone and in alcohol.

Identification—Prepare a solution of Acetophenazine Maleate in methanol containing 1 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 10 µl. of this solution and 10 µl. of a methanol solution of NF Acetophenazine Maleate Reference Standard containing 1 mg. per ml. Allow the spots to dry, and develop the chromatogram, using acetone–stronger ammonia water (95:5) as the solvent, until the solvent front has moved about three-fourths of the length of the plate. Allow the solvent to evaporate, and locate the spots using longwave ultraviolet light: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Acetophenazine Maleate, previously dried at 65° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Acetophenazine Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 30,000 solution of Acetophenazine Maleate in methanol exhibits maxima and minima at the same wavelengths as that of NF Acetophenazine Maleate Reference Standard, similarly measured, and the respective absorptivities, at the point of maximum absorbance occurring at about 243 mµ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Acetophenazine Maleate at 65° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Acetophenazine Maleate yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 500 mg. of Acetophenazine Maleate, previously dried at 65° for 4 hours and accurately weighed, in 50 ml. of glacial acetic acid, warming slightly to effect solution. Cool to room temperature, add 10 ml. of acetic anhydride, and allow to stand for 5 minutes. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green-yellow end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 32.19 mg. of $C_{23}H_{29}N_3O_2S.2C_4H_4O_4$.

Packaging and storage—Preserve Acetophenazine Maleate in tight containers.

CATEGORY—Tranquilizer (major).

USUAL DOSE—**20 mg.** three times a day.

USUAL DOSE RANGE—**40** to **80 mg.** per day.

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* Patented. See notice, page ii.

Acetophenazine Maleate Tablets

Acetophenazine Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{23}H_{29}N_3O_2S\,.\,2C_4H_4O_4$.

Identification—Heat a quantity of finely powdered Acetophenazine Maleate Tablets, equivalent to about 20 mg. of acetophenazine maleate, with 20 ml. of methanol on a steam bath for 5 minutes, with occasional swirling. Cool to room temperature, add methanol to restore to original volume, shake vigorously for 2 minutes, and filter. A 10-µl. portion of the filtrate meets the requirements of the *Identification test* under *Acetophenazine Maleate*, page 22.

Disintegration, page 878—The disintegration time limit for Acetophenazine Maleate Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Acetophenazine Maleate Tablets meet the requirements of the content uniformity test for tablets.

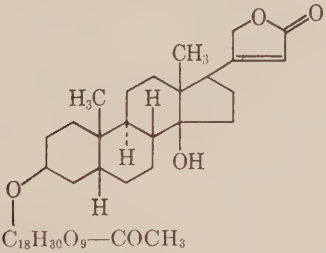
Assay—Weigh and finely powder not less than 20 Acetophenazine Maleate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of acetophenazine maleate, to a separator, add 50 ml. of sodium chloride solution (1 in 5), and sufficient sodium hydroxide solution (1 in 10) to adjust to pH 11, and allow to cool to room temperature. Extract with four 40-ml. portions of solvent hexane. Extract the combined solvent hexane extracts with three 50-ml. portions of 0.1 *N* hydrochloric acid, combining the acid extracts in a 200-ml. volumetric flask. Dilute to volume with 0.1 *N* hydrochloric acid, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Acetophenazine Maleate Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 278 mµ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{23}H_{29}N_3O_2S.2C_4H_4O_4$ in the portion of the Tablets taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Acetophenazine Maleate Tablets in tight containers.

Tablets available—Acetophenazine Maleate Tablets usually available contain the following amount of acetophenazine maleate: 20 mg.

CATEGORY and DOSE—See Acetophenazine Maleate.

Acetyldigitoxin*



(acetyltridigitoxose)

α-Digitoxin Monoacetate

$C_{43}H_{66}O_{14}$ Mol. wt. 807.00

Acetyldigitoxin contains not less than 95.0 percent and not more than 100.5 percent of $C_{43}H_{66}O_{14}$, calculated on the dried basis.

Caution: Acetyldigitoxin is extremely poisonous.

Description—Acetyldigitoxin occurs as a white, odorless, microcrystalline powder. It is hygroscopic.

Solubility—Acetyldigitoxin is soluble in methanol and sparingly soluble in chloroform. It is slightly soluble in alcohol and practically insoluble in water.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Acetyldigitoxin exhibits maxima only at the same wavelengths as that of NF Acetyldigitoxin Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Acetyldigitoxin in methanol exhibits maxima and minima at the same wavelengths as that of NF Acetyldigitoxin Reference Standard, similarly measured.

Loss on drying, page 814—Dry Acetyldigitoxin at 105° for 4 hours: it loses not more than 10 percent of its weight.

Residue on ignition, page 858—Acetyldigitoxin yields not more than 0.1 percent of residue on ignition.

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* Patented. See notice, page ii.

Assay—Transfer about 100 mg. of Acetyldigitoxin, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 5.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Acetyldigitoxin Reference Standard, in the same medium, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 217 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{43}H_{66}O_{14}$ in the Acetyldigitoxin taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Acetyldigitoxin in tight, light-resistant containers.

CATEGORY—Cardiotonic.

USUAL DOSE—Initial—rapid digitalization, **1.8 mg.** in one dose or several divided doses given within 24 hours; slow digitalization, **2.4 mg.** in divided doses given over a period of 2 to 6 days; maintenance, **150 mcg.** per day.

USUAL DOSE RANGE—Rapid digitalization, **1.6** to **2.2 mg.**; slow digitalization, **1.8** to **3.2 mg.**; maintenance, **100** to **200 mcg.**

Acetyldigitoxin Tablets

Acetyldigitoxin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{43}H_{66}O_{14}$.

Identification—Shake a quantity of powdered Acetyldigitoxin Tablets, equivalent to about 200 mcg. of acetyldigitoxin, with 10 ml. of a freshly prepared solution of *m*-dinitrobenzene in alcohol (1 in 100), and filter. Add 1 ml. of tetraethylammonium hydroxide solution (1 in 10) to the filtrate, and mix: a reddish violet color slowly forms and then fades.

Disintegration, page 878—The disintegration time limit for Acetyldigitoxin Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Acetyldigitoxin Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Weigh accurately about 40 mg. of NF Acetyldigitoxin Reference Standard, previously dried at 105° for 4 hours, and dissolve in sufficient alcohol to make 100.0 ml. Dilute 20.0 ml. of this solution to 100.0 ml. with alcohol, and mix.

Assay preparation—Weigh and finely powder not less than 20 Acetyldigitoxin Tablets. Accurately weigh a portion of the powder, equivalent to about 1 mg. of acetyldigitoxin, and transfer it to a 50-ml. glass-stoppered flask. Add about 30 ml. of chloroform-methanol mixture (2:1), and shake mechanically for 30 minutes. Filter into a 50-ml. volumetric flask, wash the original flask with several portions of the solvent mixture, and filter into the same flask. Dilute to volume with the solvent mixture, and mix. Evaporate 20.0 ml. of this solution to dryness with a rotary vacuum evaporator, using a room temperature water bath, and dissolve the residue in 5.0 ml. of alcohol.

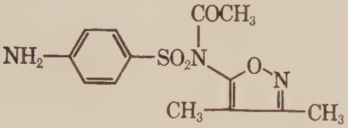
Procedure—To the *Assay preparation*, to 5.0 ml. of the *Standard preparation*, and to 5.0 ml. of alcohol to serve as the blank, add 10.0 ml. of alkaline picrate T.S., and mix by swirling. Allow the solutions to stand, protected from intense light, for 15 minutes, swirling the flasks occasionally. Concomitantly determine the absorbances of the solutions in 1-cm. cells at the maximum at about 485 mμ, with a suitable spectrophotometer, against the reagent blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{43}H_{66}O_{14}$ in the portion of Tablets taken by the formula $0.0125C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Acetyldigitoxin Tablets in well-closed containers.

Tablets available—Acetyldigitoxin Tablets usually available contain the following amounts of acetyldigitoxin: 100 and 200 mcg.

CATEGORY and DOSE—See Acetyldigitoxin.

Acetyl Sulfisoxazole*



N-(3,4-Dimethyl-5-isoxazolyl)-*N*-sulfanilylacetamide

$C_{13}H_{15}N_3O_4S$ Mol. wt. 309.35

Acetyl Sulfisoxazole contains not less than 98.0 percent and not more than 100.5 percent of $C_{13}H_{15}N_3O_4S$, calculated on the dried basis.

Description—Acetyl Sulfisoxazole occurs as a white or slightly yellow, crystalline powder.

Solubility—Acetyl Sulfisoxazole is practically insoluble in water. It is slightly soluble in alcohol, and is sparingly soluble in chloroform.

Identification—

A: Dissolve about 10 mg. of Acetyl Sulfisoxazole in 1 ml. of hydrochloric acid, and heat at 100° for 1 minute. Cool the solution, add 10 ml. of water, then add 3 drops of sodium nitrite solution (1 in 100) and 1 ml. of betanaphthol T.S.: an orange precipitate is formed.

B: Place 100 mg. of Acetyl Sulfisoxazole in a test tube, and add 2 ml. of sodium hydroxide solution (1 in 10). Boil for 2 minutes, cool, and carefully add diluted hydrochloric acid dropwise until, first, a precipitate is formed, and then until the precipitate dissolves. Neutralize the solution by adding calcium carbonate in small portions until there is no further evolution of gas. Filter, and add to the filtrate 3 drops of ferric chloride T.S.: a reddish brown color is produced.

Melting range, page 814—Acetyl Sulfisoxazole melts between 192° and 195°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Acetyl Sulfisoxazole, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Acetyl Sulfisoxazole Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Acetyl Sulfisoxazole in alcohol exhibits maxima and minima at the same wavelengths as that of NF Acetyl Sulfisoxazole Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 290 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Acetyl Sulfisoxazole at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Acetyl Sulfisoxazole yields not more than 0.1 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 200 mg. of Acetyl Sulfisoxazole meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Heavy metals, *Method II*, page 806—The heavy metals limit for Acetyl Sulfisoxazole is 20 parts per million.

Assay—Transfer about 1 g. of Acetyl Sulfisoxazole, accurately weighed, to a 250-ml. beaker. Add 15 ml. of glacial acetic acid, swirl to dissolve the sample, then add 2 ml. of sulfuric acid, 25 ml. of hydrochloric acid, and 80 ml. of water. Cool the solution, and titrate immediately with 0.1 *M* sodium nitrite, determining the end-point electrometrically, using calomel and platinum electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 30.94 mg. of $C_{13}H_{15}N_3O_4S$.

Packaging and storage—Preserve Acetyl Sulfisoxazole in tight, light-resistant containers.

CATEGORY—Antibacterial.

USUAL DOSE—Initial, **4.6 g.**, the equivalent of **4 g.** of sulfisoxazole; then **1.15 g.**, the equivalent of **1 g.** of sulfisoxazole, every 4 to 6 hours.

USUAL DOSE RANGE—**1.15 g.** to **2.3 g.** every 4 to 6 hours.

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* Patented. See notice, page ii.

Acetyl Sulfisoxazole Oral Suspension

Acetyl Sulfisoxazole Oral Suspension contains an amount of acetyl sulfisoxazole equivalent to not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{11}H_{13}N_3O_3S$ (sulfisoxazole).

Identification—Centrifuge a portion of Acetyl Sulfisoxazole Oral Suspension, wash the separated solid by centrifugation with several portions of water, and recrystallize from hot alcohol: the crystals so obtained respond to the *Identification tests*, and meet the requirements for *Ultraviolet absorption* under *Acetyl Sulfisoxazole*, page 25.

pH, page 824—The pH of Acetyl Sulfisoxazole Oral Suspension is between 5.0 and 5.5.

Assay—Transfer an accurately measured volume of Acetyl Sulfisoxazole Oral Suspension, equivalent to about 1 g. of sulfisoxazole, to a 250-ml. beaker. Add 40 ml. of hydrochloric acid, swirl until the sample is dissolved, add 100 ml. of water, and titrate immediately with 0.1 *M* sodium nitrite, determining the end-point electrometrically, using calomel and platinum electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 26.73 mg. of sulfisoxazole ($C_{11}H_{13}N_3O_3S$).

Packaging and storage—Preserve Acetyl Sulfisoxazole Oral Suspension in tight, light-resistant containers.

Suspension available—Acetyl Sulfisoxazole Oral Suspension usually available contains acetyl sulfisoxazole equivalent to the following amount of sulfisoxazole: 500 mg. in 5 ml.

CATEGORY and DOSE—See Acetyl Sulfisoxazole.

Alcohol, Isopropyl, page 382
Alcohol, Isopropyl Rubbing, page 383

Rubbing Alcohol

Rubbing Alcohol and all preparations coming under the classification of Rubbing Alcohols must be manufactured in accordance with the requirements of the Internal Revenue Service, U. S. Treasury Department, using Formula 23-H (8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone, and 100 parts by volume of ethyl alcohol). It contains not less than 68.5 percent and not more than 71.5 percent by volume of absolute ethyl alcohol, the remainder consisting of water and the denaturants, with or without color additives, and perfume oils. Rubbing Alcohol contains in each 100 ml. not less than 355 mg. of sucrose octaacetate or not less than 1.40 mg. of denatonium benzoate. The preparation may be colored with one or more color additives, listed by the Food and Drug Administration for use in drugs. A suitable stabilizer may also be added. Rubbing Alcohol complies with the requirements of the Internal Revenue Service of the United States Treasury Department.

NOTE: Rubbing Alcohol must be packaged, labeled, and sold in accordance with the regulations issued by the Internal Revenue Service, U. S. Treasury Department.

Description—Rubbing Alcohol is a transparent, colorless, or colored as desired, mobile, and volatile liquid. It has an extremely bitter taste, and in the absence of added odorous constituents, a characteristic odor. It is flammable.

Specific gravity, page 866—The specific gravity of Rubbing Alcohol manufactured with specially denatured alcohol Formula 23-H, is not less than 0.8691 and not more than 0.8771 at 15.56° (the U. S. Government standard temperature for alcohol determination).

Nonvolatile residue—

When the denaturant is sucrose octaacetate—Evaporate 25.0 ml. of Rubbing Alcohol in a tared platinum dish on a steam bath, and dry the residue at 105° for 1 hour: the weight of the residue is not less than 89 mg. Retain the residue for the *Assay for sucrose octaacetate*.

When the denaturant is denatonium benzoate—Evaporate 200.0 ml. of Rubbing Alcohol, quantitatively transferred in convenient portions, in a tared platinum dish on a steam bath, and dry the residue at 105° for 1 hour: the weight of the residue is not less than 2.8 mg. Dissolve the residue in 25 ml. of water, wash with two 15-ml. portions of ether, add 1 ml. of hydrochloric acid, and extract with three 25-ml. portions of ether. The ultraviolet absorption spectrum of the ether solution shows a maximum at about 228 mμ.

Methanol—Dilute 0.5 ml. of Rubbing Alcohol to 1 ml. with water. To 0.5 ml. of the dilution add 1 drop of dilute phosphoric acid (1 in 20), and 1 drop of potassium permanganate solution (1 in 20). Mix, allow to stand 1 minute, and add sodium bisulfite solution (1 in 20), dropwise, until the permanganate color is discharged. If a brown color remains, add 1 drop of the dilute phosphoric acid. To the colorless solution add 5 ml. of freshly prepared chromotropic acid T.S. and heat in a water bath for 10 minutes at 60°: no violet color appears.

Assay for denatonium benzoate—

Buffer solution—Dissolve 9.23 g. of anhydrous dibasic sodium phosphate in 800 ml. of water, adjust to pH 4 with saturated citric acid solution, dilute to 1000.0 ml. with water, and mix.

Standard preparation—Dissolve about 25 mg. of NF Denatonium Benzoate Reference Standard, accurately weighed, in sufficient water to make 500.0 ml., and mix.

Assay preparation—Evaporate 100.0 ml. of Rubbing Alcohol, quantitatively transferred in convenient portions, in a small conical flask on a steam bath. Dissolve the residue in the flask in 25.0 ml. of water.

Procedure—Treat the standard and the sample solutions and the blank similarly and concurrently. Transfer 10.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of *Buffer solution* to separate 250-ml. separators, and add to each 40 ml. of *Buffer solution*, 10 ml. of a solution of bromophenol blue in chloroform (1 in 1000), and 60 ml. of chloroform. Shake the separators vigorously for 2 minutes, let stand for 15 minutes, then withdraw the chloroform layers through chloroform-washed cotton into 100-ml. volumetric flasks. Repeat the extraction with 20 ml. of chloroform, adding the filtered chloroform extracts to the respective volumetric flasks, dilute to volume with chloroform, and mix. Without delay, concomitantly determine the absorbances of the solutions obtained from the *Assay preparation* (A_U) and from the *Standard preparation* (A_S), respectively, at the maximum at about 410 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Calculate the quantity, in mg., of denatonium benzoate ($C_{28}H_{34}N_2O_3$) in 100 ml. of Rubbing Alcohol by the formula $0.025C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Assay for sucrose octaacetate—Using about 50 ml. of 70 percent alcohol, transfer quantitatively the residue from the test for *Nonvolatile residue* into a 500-ml. conical flask. Neutralize the solution with 0.1 *N* sodium hydroxide, using phenolphthalein T.S. as the indicator. Add 25.0 ml. of 0.1 *N* sodium hydroxide, attach an air condenser to the flask, and reflux on a steam bath for 1 hour. Remove from the steam bath, cool quickly, and titrate the excess alkali with 0.1 *N* sulfuric acid, using phenolphthalein T.S. as the indicator. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* sodium hydroxide is equivalent to 8.483 mg. of sucrose octaacetate ($C_{28}H_{38}O_{19}$).

Packaging and storage—Preserve Rubbing Alcohol in tight containers remote from fire.

CATEGORY—Rubefacient.

Alginate, Sodium, page 636

Almond Oil

Almond Oil is the fixed oil obtained by expression from the kernels of varieties of *Prunus amygdalus* Batsch (Fam. *Rosaceæ*).

Description—Almond Oil is a clear, pale straw-colored or colorless, oily liquid. It is almost odorless, and has a bland taste. It remains clear at −10°, and does not congeal until cooled to nearly −20°.

Solubility—Almond Oil is slightly soluble in alcohol, but is miscible with ether, with chloroform, with benzene, and with solvent hexane.

Specific gravity, page 866—The specific gravity of Almond Oil is not less than 0.910 and not more than 0.915.

Foreign kernel oils—Shake vigorously for 5 minutes 2 ml. of Almond Oil with a mixture of 1 ml. of fuming nitric acid and 1 ml. of water: the mixture is not more than slightly colored.

Cottonseed oil—Mix 5 ml. of Almond Oil in a test tube with 5 ml. of a mixture of equal volumes of amyl alcohol and of a 1 per cent solution of sulfur in carbon disulfide, warm the mixture carefully until the carbon disulfide is expelled, and immerse the test tube to one-third of its length in a boiling, saturated solution of sodium chloride: the mixture develops no reddish color within 2 hours.

Sesame oil—Mix 10 ml. of Almond Oil with 10 ml. of hydrochloric acid, add 0.1 ml. of an alcohol solution of furfural (1 in 50), and shake the mixture vigorously for 15 seconds: no pink to crimson color appears in the acid layer when separate layers form. Should any color appear in the acid layer, add 10 ml. of water, and again shake the mixture vigorously. In the absence of sesame oil the pink color is fugitive.

Mineral oil and foreign fatty oils—Heat on a steam bath 10 ml. of Almond Oil with 15 ml. of a solution of sodium hydroxide (1 in 6) and 30 ml. of alcohol in a flask which has a small, short-stemmed funnel inserted in the neck, and occasionally agitate the mixture until it becomes clear. Transfer the solution to a shallow dish, evaporate the alcohol on a steam bath, and mix the residue with 100 ml. of water: a clear solution results (*absence of mineral oil*). Add an excess of hydrochloric acid to this solution, remove the layer of fatty acids which rises to the surface, wash it with warm water, clarify it by heating on a steam bath, and allow it to cool to 15° without stirring: the fatty acids remain clear for 30 minutes at this temperature (*absence of foreign fatty oils*).

Foreign oils—One volume of the mixed fatty acids obtained in the test for *Mineral oil and foreign fatty oils* when mixed with 1 volume of alcohol, yields a clear solution, which at 15° does not deposit any fatty acid or become turbid upon the further addition of 1 volume of alcohol (*absence of olive, peanut,* or *other fixed oils*).

Free fatty acids, page 804—The free fatty acids in 10 g. of Almond Oil require for neutralization not more than 5 ml. of 0.1 *N* sodium hydroxide.

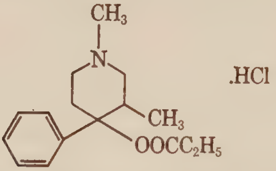
Iodine value, page 804—The iodine value of Almond Oil is not less than 95 and not more than 105.

Saponification value, page 805—The saponification value of Almond Oil is not less than 190 and not more than 200.

Packaging and storage—Preserve Almond Oil in tight containers.

CATEGORY—Emollient; perfume.

Alphaprodine Hydrochloride



(±)-1,3-Dimethyl-4-phenyl-4-piperidinol Propionate Hydrochloride

$C_{16}H_{23}NO_2.HCl$ Mol. wt. 297.83

Alphaprodine Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{16}H_{23}NO_2.HCl$, calculated on the dried basis.

Description—Alphaprodine Hydrochloride occurs as a white, crystalline powder. It has a slight odor.

Solubility—Alphaprodine Hydrochloride is freely soluble in water, in alcohol, and in chloroform. It is insoluble in ether.

Identification—

A: Mix about 2 mg. of Alphaprodine Hydrochloride on a spot plate with 1 drop of ammonium thiocyanate T.S. and 1 drop of cupric sulfate solution (1 in 100): a brown turbidity results.

B: Mix about 2 mg. of Alphaprodine Hydrochloride on a spot plate with 1 drop of sulfuric acid-formaldehyde T.S.: an orange-red color develops.

C: A solution of Alphaprodine Hydrochloride in water responds to the tests for *Chloride,* page 808.

Melting range, page 814—Alphaprodine Hydrochloride melts between 218° and 220°.

Loss on drying, page 814—Dry Alphaprodine Hydrochloride at 80° in vacuum over phosphorus pentoxide for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Alphaprodine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Alphaprodine Hydrochloride in 20 ml. of water, add 2 ml. of diluted acetic acid, and dilute with water to 25 ml.: the heavy metals limit for Alphaprodine Hydrochloride is 20 parts per million.

Assay—Dissolve about 600 mg. of Alphaprodine Hydrochloride, accurately weighed, in a mixture of 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 29.78 mg. of $C_{16}H_{23}NO_2.HCl$.

Packaging and storage—Preserve Alphaprodine Hydrochloride in well-closed containers.

CATEGORY—Analgesic (narcotic).

USUAL DOSE—Subcutaneous, **20** to **40 mg.** Intravenous, **20 mg.**

USUAL DOSE RANGE—Subcutaneous, **20** to **60 mg.** Intravenous, **20** to **30 mg.**

Alphaprodine Hydrochloride Injection

Alphaprodine Hydrochloride Injection is a sterile solution of alphaprodine hydrochloride in water for injection. It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{16}H_{23}NO_2 . HCl$.

Identification—

A: To 1 ml. of Alphaprodine Hydrochloride Injection add 2 drops of ammonium thiocyanate T.S. and 1 drop of cupric sulfate solution (1 in 100): a brown turbidity results.

B: Evaporate to dryness a few drops of Alphaprodine Hydrochloride Injection in a small porcelain crucible and add 0.5 ml. of sulfuric acid-formaldehyde T.S.: an orange-red color develops.

pH, page 824—The pH of Alphaprodine Hydrochloride Injection is between 4.0 and 6.0.

Other requirements—Alphaprodine Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—Transfer to a 125-ml. separator an accurately measured volume of Alphaprodine Hydrochloride Injection, equivalent to about 900 mg. of alphaprodine hydrochloride. Add 5 ml. of sodium hydroxide T.S. and extract the alphaprodine, first with 50 ml. and then with 25 ml. of chloroform, passing the extracts through a filter containing 25 g. of anhydrous sodium sulfate, into a 250-ml. flask. Wash the sodium sulfate with 25 ml. of chloroform, collecting the washings in the 250-ml. flask, add 4 drops of methyl red T.S., and titrate with 0.1 *N* perchloric acid in dioxane to a red end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 29.78 mg. of $C_{16}H_{23}NO_2.HCl$.

Packaging and storage—Preserve Alphaprodine Hydrochloride Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Alphaprodine Hydrochloride Injection usually available contains the following amounts of alphaprodine hydrochloride: 40 mg. in 1 ml., 60 mg. in 1 ml., and 600 mg. in 10 ml.

CATEGORY and DOSE—See Alphaprodine Hydrochloride.

Alum

Aluminum Ammonium Sulfate

$AlNH_4(SO_4)_2 . 12H_2O$ Mol. wt. 453.33

Aluminum Potassium Sulfate

$AlK(SO_4)_2 . 12H_2O$ Mol. wt. 474.39

Alum, previously dried at 250° to constant weight, contains not less than 99.0 percent and not more than 100.5 percent of $AlNH_4(SO_4)_2$, or not less than 99.0 percent and not more than 100.5 percent of $AlK(SO_4)_2$.

The label of the container must indicate whether the salt is Ammonium Alum or Potassium Alum.

Description—Alum occurs as large, colorless crystals, crystalline fragments, or as a white powder. Alum is odorless, and has a sweetish, strongly astringent taste. Its solutions are acid to litmus.

Solubility—Alum is freely soluble in water and very soluble in boiling water. Alum is insoluble in alcohol. It is freely but slowly soluble in glycerin.

Identification—

A: Add sodium hydroxide T.S. dropwise to a solution of Ammonium Alum (1 in 20): a precipitate forms which dissolves in an excess of the reagent, and ammonia is evolved.

B: Add sodium hydroxide T.S. dropwise to a solution of Potassium Alum (1 in 20): a precipitate forms which dissolves in an excess of the reagent, but no ammonia is evolved.

C: Hold Potassium Alum in a nonluminous flame: a violet color is imparted to the flame.

D: Add 10 ml. of sodium bitartrate T.S. to 5 ml. of a saturated solution of Potassium Alum: a white, crystalline precipitate forms within 30 minutes.

E: A solution of Alum (1 in 20) responds to the tests for *Aluminum,* page 807, and for *Sulfate,* page 810.

Loss on drying, page 814—Dry Alum at 250° to constant weight, powder the sample, and dry again to constant weight: Ammonium Alum loses not less than 45 percent and not more than 48 percent of its weight, and Potassium Alum loses not less than 43 percent and not more than 46 percent of its weight.

Alkalies and alkaline earths—Completely precipitate the aluminum from a boiling solution of 1 g. of Ammonium Alum in 100 ml. of water by the addition of enough ammonia T.S. to render the solution distinctly alkaline to methyl red T.S., and filter. Evaporate the filtrate to dryness, and ignite: the weight of the residue does not exceed 5 mg. (0.5 percent).

Arsenic—A solution of 1.25 g. of Alum in water meets the requirements of the *Arsenic Test*, page 777 (8 parts per million As).

Heavy metals—Dissolve 1 g. of Alum in sufficient water to make 20 ml., and add 5 ml. of 0.1 *N* hydrochloric acid. Evaporate the sample to dryness in a porcelain evaporating dish. Treat the residue with 20 ml. of water and add 50 mg. of hydroxylamine hydrochloride. Heat the solution on a steam bath for 10 minutes, cool, dilute to 25 ml., and proceed as directed in the *Heavy Metals Test*, page 806, but add 50 mg. of hydroxylamine hydrochloride to the standard lead solution: the heavy metals limit for Alum is 20 parts per million.

Iron—Add 5 drops of potassium ferrocyanide T.S. to 20 ml. of a solution of Alum (1 in 150): no blue color is produced immediately.

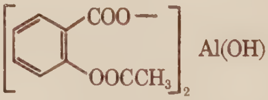
Assay—Weigh accurately about 500 mg. of Alum, previously dried at 250° to constant weight, powder the sample, and dry again to constant weight, moisten with 1 ml. of glacial acetic acid, and add 50 ml. of water and 50.0 ml. of 0.05 *M* disodium ethylenediaminetetraacetate. Warm on a steam bath until solution is complete, and boil gently for 5 minutes. Cool, add 20 ml. of acetic acid-ammonium acetate buffer T.S., 50 ml. of alcohol, and 2 ml. of dithizone T.S., and titrate with 0.05 *M* zinc sulfate to a bright rose-pink color. Perform a blank determination, and make any necessary correction. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 11.85 mg. of $AlNH_4(SO_4)_2$ or 12.91 mg. of $AlK(SO_4)_2$.

Packaging and storage—Preserve Alum in well-closed containers.

CATEGORY—Local astringent.

FOR EXTERNAL USE—Topically as a 0.5 to 5 percent solution.

Aluminum Aspirin



Hydroxybis(salicylato)aluminum Diacetate

$C_{18}H_{15}AlO_9$ Mol. wt. 402.30

Aluminum Aspirin contains not less than the equivalent of 80.0 percent of $C_9H_8O_4$ (aspirin), calculated on the anhydrous basis, corresponding to not less than 90.0 percent of $C_{18}H_{15}AlO_9$. Aluminum Aspirin yields not less than 12.0 percent and not more than 17.0 percent of Al_2O_3 (aluminum oxide), calculated on the anhydrous basis.

Description—Aluminum Aspirin occurs as a white to off-white powder or granules. It is odorless, or has only a slight odor.

Solubility—Aluminum Aspirin is insoluble in water and organic solvents. It is soluble, with decomposition, in aqueous solutions of alkali hydroxides and carbonates.

Identification—

A: Dissolve 100 mg. of Aluminum Aspirin in 10 ml. of sodium hydroxide T.S., heating, if necessary, to complete solution. Acidify a portion of the solution with hydrochloric acid, and add 1 or 2 drops of ferric chloride T.S.: a violet-red color is produced.

B: Ignite about 2 g. of Aluminum Aspirin in a suitable crucible, until thoroughly charred, cool, moisten the residue with 1 ml. of sulfuric acid, and cautiously ignite until the carbon is completely consumed, repeating the ignition with additional sulfuric acid, if necessary. Transfer the residue to a platinum crucible, add 1 g. of anhydrous sodium carbonate and ignite for 20 minutes (the mass should be completely molten). Cool, dissolve the mass in diluted hydrochloric acid, and filter: the filtrate responds to the tests for *Aluminum*, page 807.

Water, page 900—Determine the water

content of Aluminum Aspirin by the titrimetric method, stirring the sample for 7 minutes prior to titration and recording the end-point at the end of 10 minutes, accurately timed, from the addition of the sample to the titration flask. Perform a blank determination, following the same time schedule, and make any necessary correction: it contains not more than 8 percent of water.

Heavy metals, *Method II*, page 806—The heavy metals limit for Aluminum Aspirin is 10 parts per million.

Limit of salicylate—Using the absorbance values found at 308 mμ in the *Assay for aspirin* for the *Sample preparation* (A_{U308}) and for the *Standard salicylic acid solution* (A_{S308}), calculate the percent salicylate content (as salicylic acid) by the formula $200 \times (C_S/W) \times (A_{U308}/A_{S308})$, in which C_S is the exact concentration, in mcg. per ml., of USP Salicylic Acid in the *Standard salicylic acid solution*, W is the weight, in mg., of the sample taken, and A_{S308} and A_{U308} are as defined in the *Assay for aspirin*. The salicylate content is not more than 7.5 percent, calculated on the anhydrous basis.

Assay for aluminum oxide—Transfer about 1 g. of Aluminum Aspirin, accurately weighed, to a previously tared and ignited crucible. Ignite the sample at 1000°, preferably in a muffle furnace, to constant weight. The ignited residue obtained is Al_2O_3.

Assay for aspirin—

Sample preparation—Transfer to a 250-ml. separator about 150 mg. of Aluminum Aspirin, accurately weighed, add 40 ml. of sodium fluoride-hydrochloric acid solution (dissolve 500 mg. of sodium fluoride in 100 ml. of 0.1 *N* hydrochloric acid), and shake for 5 minutes. Allow the solution to stand for 10 minutes with frequent shaking. Extract the solution with six 20-ml. portions of chloroform, filtering each portion into a 200-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Standard aspirin solution—Dissolve an accurately weighed quantity of USP Aspirin Reference Standard in chloroform, and dilute it, quantitatively and stepwise, to obtain a *Standard aspirin solution* having a concentration of about 50 mcg. per ml.

Standard salicylic acid solution—Dissolve an accurately weighed quantity of salicylic acid in chloroform, and dilute it, quantitatively and stepwise, to obtain a *Standard salicylic acid solution* having a concentration of about 25 mcg. per ml.

Procedure—Concomitantly determine the absorbances of the *Sample preparation* at 278 mμ and at 308 mμ, of the *Standard aspirin solution* at 278 mμ, and of the *Standard salicylic acid solution* at 278 mμ and at 308 mμ, in 1-cm. cells, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_9H_8O_4$ (aspirin) in the Aluminum Aspirin taken by the formula, $2C_A \times [A_{U278} - A_{U308}(A_{S278}/A_{S308})]/A_{A278}$, in which C_A is the exact concentration, in mcg. per ml., of USP Aspirin Reference Standard in the *Standard aspirin solution*, and A_U, A_S, and A_A are the absorbances of the *Sample preparation*, *Standard salicylic acid solution*, and *Standard aspirin solution*, respectively, at the wavelengths designated by the subscripts.

Packaging and storage—Preserve Aluminum Aspirin in well-closed containers in a cold place.

Category—Analgesic.

Usual dose—**670 mg.**, equivalent to about **600 mg.** of aspirin, every 4 hours as necessary. Children's dose—**75 mg.** every 4 hours.

Aluminum Aspirin Tablets

Aluminum Aspirin Tablets contain an amount of $C_{18}H_{15}AlO_9$ (aluminum aspirin) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_8O_4$ (aspirin).

Identification—

A: Digest a portion of powdered Aluminum Aspirin Tablets, equivalent to about 100 mg. of aluminum aspirin, with 10 ml. of sodium hydroxide T.S. with gentle warming, and filter. The filtrate responds to *Identification test A* under *Aluminum Aspirin*, page 30.

B: A portion of powdered Aluminum Aspirin Tablets, equivalent to about 2 g. of aluminum aspirin, responds to *Identification test B* under *Aluminum Aspirin*, page 30.

Disintegration, page 878—The disintegration time limit for Aluminum Aspirin Tablets is 5 minutes.

Weight variation, page 901—Aluminum Aspirin Tablets meet the requirements of the weight variation test for tablets.

Salicylate—Using the absorbance values found at 308 mμ in the *Assay* for the *Sample preparation* (A_{U308}) and the *Standard salicylic acid solution* (A_{S308}), calculate the percent salicylate content (as salicylic acid) of the labeled aspirin content by the formula $(200/T) \times$ (Av. Wt. per Tablet/

Wt. of Sample) $\times C_S \times (A_{U308}/A_{S308})$, in which T is the labeled quantity of aspirin, in mg., in the tablet, C_S is the exact concentration, in mcg. per ml., of salicylic acid in the *Standard salicylic acid solution,* and A_{U308} and A_{S308} are as defined in the *Assay:* the salicylate content is not more than 15.0 percent of the labeled aspirin content.

Assay—Weigh and finely powder not less than 20 Aluminum Aspirin Tablets, and proceed as directed in the *Assay for Aspirin* under *Aluminum Aspirin,* page 30, using an accurately weighed portion of the powder, equivalent to about 150 mg. of aspirin. Calculate the quantity, in mg., of $C_9H_8O_4$ per tablet by the formula $2 \times$ (Av. Wt. per Tablet/Wt. of Sample) $\times C_A \times [A_{U278} - A_{U308} (A_{S278}/A_{S308})]/A_{A278}$, in which C_A is the exact concentration, in mcg. per ml., of USP Aspirin Reference Standard in the *Standard aspirin solution,* and A_U, A_S, and A_A are the absorbances of the *Sample preparation, Standard salicylic acid solution,* and the *Standard aspirin solution,* respectively, at the wavelengths designated by the subscripts.

Packaging and storage—Preserve Aluminum Aspirin Tablets in well-closed containers.

Tablets available—Aluminum Aspirin Tablets usually available contain the equivalent of the following amount of aspirin: 75 mg.

CATEGORY and DOSE—See Aluminum Aspirin.

Aluminum Chloride

$AlCl_3 . 6H_2O$ Mol. wt. 241.43

Aluminum Chloride contains not less than 95.0 percent and not more than 102.0 percent of $AlCl_3$, calculated on the anhydrous basis.

Description—Aluminum Chloride occurs as a white or yellowish white, deliquescent, crystalline powder. It is nearly odorless and has a sweet, very astringent taste. Its solutions are acid to litmus.

Solubility—Aluminum Chloride is very soluble in water and is freely soluble in alcohol. It is soluble in glycerin.

Identification—A solution of Aluminum Chloride (1 in 10) responds to the tests for *Aluminum,* page 807, and for *Chloride,* page 808.

Water, page 900—Determine the water content of Aluminum Chloride by the titrimetric method (*Residual Titration* procedure): not less than 44 percent and not more than 50 percent is found.

Sulfate—The addition of 0.2 ml. of barium chloride T.S. to 10 ml. of a solution of Aluminum Chloride (1 in 100) produces no turbidity in 1 minute.

Alkalies and alkaline earths—To a boiling solution of 1 g. of Aluminum Chloride in 150 ml. of water, add a few drops of methyl red T.S., then add ammonia T.S. until the color of the solution just changes to a distinct yellow. Add hot water to restore the volume to 150 ml., and filter while hot. Evaporate 75 ml. of the filtrate to dryness, and ignite to constant weight: the weight of the residue does not exceed 2.5 mg. (0.5 percent).

Arsenic—A solution of 1.25 g. of Aluminum Chloride in water meets the requirements of the *Arsenic Test,* page 777(8 parts per million As).

Heavy metals, page 806—Dissolve 1 g. of Aluminum Chloride in 1 ml. of diluted acetic acid and sufficient water to make 25 ml.: the heavy metals limit for Aluminum Chloride is 20 parts per million.

Iron—Dissolve 2 g. of Aluminum Chloride in 40 ml. of water, add 2 ml. of hydrochloric acid, dilute to 50 ml., and add 30 to 50 mg. of ammonium persulfate crystals and 5 ml. of ammonium thiocyanate T.S.: any red color in the sample solution does not exceed that in a standard of the same volume containing 20 mcg. of iron and the quantities of reagents used in the test (10 parts per million).

Assay—Transfer to a 250-ml. volumetric flask about 5 g. of Aluminum Chloride, accurately weighed, dissolve in water, dilute to volume with water, and mix. Pipet 10.0 ml. of the solution into a 250-ml. beaker, add 25.0 ml. of 0.05 *M* disodium ethylenediaminetetraacetate, and boil gently for 5 minutes. Cool, and add in the order given and with continuous stirring 20 ml. of acetic acid-ammonium acetate buffer T.S., 50 ml. of alcohol, and 2 ml. of dithizone T.S. Titrate with 0.05 *M* zinc sulfate to a bright rose-pink color. Perform a blank determination, substituting 10 ml. of water for the sample, and make any necessary correction. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 6.667 mg. of $AlCl_3$.

Packaging and storage—Preserve Aluminum Chloride in tight containers.

Category—Local astringent.

For external use—Topically as a 10 to 25 percent solution.

Aluminum Phosphate Gel

Aluminum Phosphate Gel is a water suspension containing not less than 4.0 percent and not more than 5.0 percent (w/w) of $AlPO_4$ (aluminum phosphate). It may contain sodium benzoate, benzoic acid, or other suitable agents, in an amount not exceeding 0.5 percent, as a preservative.

Description—Aluminum Phosphate Gel is a white, viscous suspension from which small amounts of water may separate on standing.

Identification—

A: A solution of Aluminum Phosphate Gel in hydrochloric acid responds to the tests for *Aluminum*, page 807.

B: A solution of Aluminum Phosphate Gel in diluted nitric acid responds to the tests for *Phosphate*, page 809.

pH, page 824—The pH of Aluminum Phosphate Gel is between 6.0 and 7.2.

Neutralization rate—Add 30 ml. of 0.1 *N* hydrochloric acid to 6 g. of Aluminum Phosphate Gel, and heat at 37° for 15 minutes: the pH of the mixture is between 2.0 and 2.5.

Acid-consuming capacity—To about 250 mg. of Aluminum Phosphate Gel, accurately weighed, add 30.0 ml. of 0.1 *N* hydrochloric acid, and digest at 37° for 30 minutes. Add 1 drop of thymol blue T.S., and titrate the excess acid with 0.1 *N* sodium hydroxide to pH 2.5. The volume of 0.1 *N* hydrochloric acid consumed is not less than 6 ml. and not more than 11 ml. for each g. of Aluminum Phosphate Gel.

Chloride—Transfer 25 g. of Aluminum Phosphate Gel to a beaker with the aid of about 50 ml. of water, add 5 ml. of nitric acid, mix well, then add, with stirring, 30.0 ml. of 0.1 *N* silver nitrate. Warm on a steam bath for 30 minutes, filter, and wash the precipitate with water acidified with nitric acid. To the filtrate add ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 3.545 mg. of Cl. Not more than 0.16 percent of Cl is found.

Soluble phosphate—Filter 20 g. of Aluminum Phosphate Gel, and wash the residue with 30 ml. of water. Add to the filtrate 2 ml. of nitric acid, heat to 60°, and add 20 ml. of ammonium molybdate T.S. Heat at 50° for 30 minutes, filter, wash the precipitate with dilute nitric acid (1 in 36), and then with potassium nitrate solution (1 in 100) until the last portion of filtrate is not acid to litmus paper. Dissolve the precipitate in 50.0 ml. of 0.1 *N* sodium hydroxide, add phenolphthalein T.S., and titrate the excess alkali with 0.1 *N* hydrochloric acid. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 0.413 mg. of PO_4. The soluble phosphate, calculated as PO_4, does not exceed 0.07 percent.

Sulfate, page 784—Add 10 ml. of diluted hydrochloric acid to 10 g. of Aluminum Phosphate Gel, and heat to boiling. Cool, dilute to 250 ml., and filter, if necessary. A 10-ml. portion of the solution shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (0.05 percent).

Arsenic—Dissolve 16.7 g. of Aluminum Phosphate Gel in just sufficient diluted hydrochloric acid. The solution meets the requirements of the *Arsenic Test,* page 777 (0.6 part per million As).

Heavy metals, page 806—Dissolve 10 g. of Aluminum Phosphate Gel in 2.5 ml. of diluted hydrochloric acid, warming if necessary, and dilute to 25 ml. with water: the heavy metals limit for Aluminum Phosphate Gel is 5 parts per million.

Assay—To about 20 g. of Aluminum Phosphate Gel, accurately weighed in a 100-ml. volumetric flask, add nitric acid to effect solution, dilute with water to volume, and mix thoroughly. Transfer 10.0 ml. of this solution to a 400-ml. beaker, dilute with water to 100 ml., heat to 60°, add an excess of ammonium molybdate T.S., and keep at 50° for 30 minutes. Filter, and wash the precipitate with dilute nitric acid (1 in 36), followed by potassium nitrate solution (1 in 100) until the last portion of filtrate is not acid to litmus paper. Dissolve the precipitate in 50.0 ml. of 0.5 *N* sodium hydroxide, add 3 drops of phenolphthalein T.S., and titrate the excess sodium hydroxide with 0.5 *N* sulfuric acid. Each ml. of 0.5 *N* sodium hydroxide is equivalent to 2.651 mg. of $AlPO_4$.

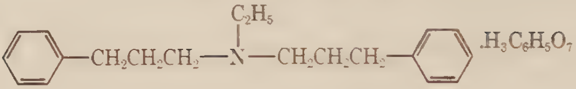
Packaging and storage—Preserve Aluminum Phosphate Gel in tight containers.

Category—Antacid.

Usual dose—**15 ml.** to **30 ml.** every 2 hours.

Usual dose range—**15** to **45 ml.**

Alverine Citrate



N-Ethyl-3,3′-diphenyldipropylamine Citrate (1:1)

$C_{20}H_{27}N . C_6H_8O_7$ Mol. wt. 473.57

Alverine Citrate contains not less than 99.0 percent and not more than 102.0 percent of $C_{20}H_{27}N . C_6H_8O_7$, calculated on the dried basis.

Description—Alverine Citrate occurs as a white to off-white powder having a sweet odor and a slightly bitter taste.

Solubility—Alverine Citrate is slightly soluble in water and in chloroform. It is sparingly soluble in alcohol, and is very slightly soluble in ether.

Identification—Suspend about 500 mg. of Alverine Citrate in 10 ml. of water, add a slight excess of sodium hydroxide T.S. to liberate the base, allow to stand for 5 minutes with occasional swirling, and filter: the filtrate responds to the tests for *Citrate*, page 808.

Melting range, page 814—Alverine Citrate melts between 100° and 102°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Alverine Citrate, previously dried at 80° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Alverine Citrate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 1500 solution of Alverine Citrate in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Alverine Citrate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance at about 258 mμ, do not differ by more than 2 percent.

pH, page 824—The pH of a solution of Alverine Citrate (1 in 200) is between 3.5 and 4.5.

Loss on drying, page 814—Dry Alverine Citrate at 80° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Alverine Citrate yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 360 mg. of Alverine Citrate, accurately weighed, to a separator, add 25 ml. of water and 5 ml. of sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water, and filter the chloroform solution through a layer of chloroform-moistened cotton layered over with anhydrous sodium sulfate, collecting the filtrate in a beaker. Wash the aqueous phase with 10 ml. of chloroform and filter as before into the beaker. To the beaker add 3 drops of methanolic methyl red T.S., and titrate with 0.1 *N* perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 47.36 mg. of $C_{20}H_{27}N . C_6H_8O_7$.

Packaging and storage—Preserve Alverine Citrate in tight, light-resistant containers.

CATEGORY Anticholinergic.

USUAL DOSE RANGE—**120 mg.** one to three times a day.

Alverine Citrate Tablets

Alverine Citrate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{20}H_{27}N . C_6H_8O_7$.

Identification—Transfer an amount of powdered Alverine Citrate Tablets, equivalent to about 120 mg. of alverine citrate, to a 200-ml. volumetric flask, add 100 ml. of 0.1 *N* hydrochloric acid, and allow to stand unstoppered until the effervescence ceases. Shake for 30 minutes, dilute to volume with 0.1 *N* hydrochloric acid, mix, and filter, discarding the first 20 ml. of filtrate: the ultraviolet absorption spectrum of the subsequent filtrate exhibits maxima and minima at the same wavelengths as that of a 1 in 1500 solution of NF Alverine Citrate Reference Standard in 0.1 *N* hydrochloric acid.

Disintegration, page 878—The disintegration time limit for Alverine Citrate Tablets is 20 minutes.

Weight variation, page 901—Alverine Citrate Tablets meet the requirements of the weight variation test for tablets.

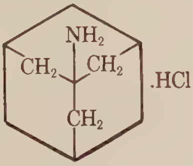
Assay—Weigh and finely powder not less than 20 Alverine Citrate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 360 mg. of alverine citrate to a separator, and continue as directed in the *Assay* under *Alverine Citrate*, page 34, beginning with "... add 25 ml. of water and 5 ml. of sodium hydroxide T.S. ... "

Packaging and storage—Preserve Alverine Citrate Tablets in tight, light-resistant containers.

Tablets available—Alverine Citrate Tablets usually available contain the following amount of alverine citrate: 120 mg.

CATEGORY and DOSE—See Alverine Citrate.

Amantadine Hydrochloride*



1-Adamantanamine Hydrochloride

$C_{10}H_{17}N.HCl$ Mol. wt. 187.71

Amantadine Hydrochloride contains not less than 98.5 percent and not more than 101.5 percent of $C_{10}H_{17}N.HCl$.

Description—Amantadine Hydrochloride occurs as a white or nearly white, odorless, crystalline powder. It has a bitter taste.

Solubility—Amantadine Hydrochloride is freely soluble in water and is soluble in alcohol and in chloroform.

Identification—Mix 100 mg. of Amantadine Hydrochloride with 1 ml. of pyridine and 0.1 ml. of acetic anhydride, and heat to boiling for about 10 seconds. Pour the hot solution into 10 ml. of 2 *N* hydrochloric acid, and cool to 5°. Collect the precipitate on a sintered-glass filter, wash with water, and dry at 60° in vacuum for 1 hour: the 1-acetamidoadamantane so obtained melts between 147° and 150°, page 814.

Clarity and color of solution—Dissolve 2 g. of Amantadine Hydrochloride in 10 ml. of water: the solution is clear and nearly colorless.

pH, page 824—The pH of a 1 in 5 solution of Amantadine Hydrochloride is between 3.5 and 5.0.

Heavy metals, page 806—Dissolve 1 g. of Amantadine Hydrochloride in 24 ml. of water and add 1 ml. of diluted acetic acid: the heavy metals limit for Amantadine Hydrochloride is 5 parts per million.

Assay—Dissolve about 120 mg. of Amantadine Hydrochloride, accurately weighed, in a mixture of 30 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S. Add 6 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 18.77 mg. of $C_{10}H_{17}N.HCl$.

Packaging and storage—Preserve Amantadine Hydrochloride in well-closed containers.

CATEGORY—Antiviral (prophylactic).

USUAL DOSE—**200 mg.** per day, given as a single dose or in two divided doses.

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* Patented. See notice, page ii.

Amantadine Hydrochloride Capsules

Amantadine Hydrochloride Capsules contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{17}N.HCl$.

Identification—Place the contents of one Amantadine Hydrochloride Capsule in a test tube, add 2 ml. of pentane, and shake well. Collect the undissolved solid on a sintered-glass filter, wash with two 1-ml. portions of pentane, and dry in the air: the amantadine hydrochloride so obtained responds to the *Identification test* under *Amantadine Hydrochloride*, page 35.

Content uniformity, *Method I*, page 798—Amantadine Hydrochloride Capsules meet the requirements of the content uniformity test for capsules.

Assay—Dissolve 10 Amantadine Hydrochloride Capsules in 20 ml of water by warming on a steam bath, with shaking. Cool, add 20 ml. of 5 *N* sodium hydroxide and 100.0 ml. of benzene, stopper, and shake gently for 15 minutes. Centrifuge to separate the layers, and transfer 10.0 ml. of the supernatant liquid to a conical flask. Add 30 ml. of glacial acetic acid, and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically, using suitable electrodes. Each ml. of 0.1 *N* perchloric acid is equivalent to 18.77 mg. of $C_{10}H_{17}N.HCl$.

Packaging and storage—Preserve Amantadine Hydrochloride Capsules in tight containers.

Capsules available—Amantadine Hydrochloride Capsules usually available contain the following amount of amantadine hydrochloride: 100 mg.

CATEGORY and DOSE—See Amantadine Hydrochloride.

Amantadine Hydrochloride Syrup

Amantadine Hydrochloride Syrup contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{17}N.HCl$.

Identification—To 10 ml. of Amantadine Hydrochloride Syrup add 5 ml. of 5 *N* sodium hydroxide and 10 ml. of benzene. Shake the mixture gently for 15 minutes, remove the benzene layer, dry it over anhydrous magnesium sulfate, and filter. To the filtrate add 1 ml. of pyridine and 0.1 ml. of acetic anhydride, and evaporate almost to dryness on a steam bath. Dissolve the residue in 5 ml. of 2 *N* hydrochloric acid by boiling, and cool to 5°. Collect the precipitate on a sintered-glass filter, wash with small portions of water, and dry at 60° in vacuum for 1 hour: the 1-acetamidoadamantane so obtained melts between 147° and 150°, page 814.

Assay—Transfer an accurately measured volume of Amantadine Hydrochloride Syrup, equivalent to about 200 mg. of amantadine hydrochloride, to a separator, add 5 ml. of 5 *N* sodium hydroxide and 20.0 ml. of benzene, shake vigorously for 15 minutes, and allow the layers to separate. Transfer 10.0 ml. of the benzene layer to a beaker containing 30 ml. of glacial acetic acid, add 6 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 18.77 mg. of $C_{10}H_{17}N.HCl$ in the benzene aliquot taken.

Packaging and storage—Preserve Amantadine Hydrochloride Syrup in tight containers.

Syrup available—Amantadine Hydrochloride Syrup usually available contains the following amount of amantadine hydrochloride: 50 mg. in 5 ml.

CATEGORY and DOSE—See Amantadine Hydrochloride.

Compound Amaranth Solution

Amaranth Solution	**90 ml.**
Caramel	**100 g.**
Alcohol	**250 ml.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

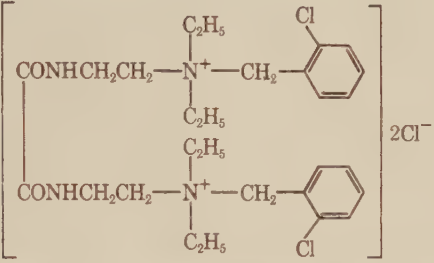
Dissolve the caramel in 500 ml. of purified water, add the amaranth solution, the alcohol, and sufficient purified water to make the product measure 1000 ml., and mix well.

Alcohol content, page 772—Compound Amaranth Solution contains from 22 to 25 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Compound Amaranth Solution in tight, light-resistant containers.

CATEGORY—Color.

Ambenonium Chloride*



[Oxalylbis(iminoethylene)]bis[(*o*-chlorobenzyl)diethylammonium] Dichloride

$C_{28}H_{42}Cl_4N_4O_2$ Mol. wt. 608.48

Ambenonium Chloride is anhydrous or may occur as the tetrahydrate. It contains not less than 97.0 percent and not more than 103.0 percent of $C_{28}H_{42}Cl_4N_4O_2$, calculated on the dried basis.

Description—Ambenonium Chloride occurs as a white, odorless powder. It melts at about 200°.

Solubility—Ambenonium Chloride is soluble in water and in alcohol, is slightly soluble in chloroform, and is practically insoluble in ether and in acetone.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Ambenonium Chloride, previously dried to constant weight at 105°, exhibits maxima only at the same wavelengths as that of NF Ambenonium Chloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2500 solution of Ambenonium Chloride in methanol exhibits maxima and minima at the same wavelengths as that of NF Ambenonium Chloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 278 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Ambenonium Chloride to constant weight at 105°: it loses not more than 11.5 percent of its weight.

Residue on ignition, page 858—Ambenonium Chloride yields not more than 0.2 percent of residue on ignition.

Assay—Dissolve about 500 mg. of Ambenonium Chloride, accurately weighed, in a mixture of 80 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 30.42 mg. of $C_{28}H_{42}Cl_4N_4O_2$.

Packaging and storage—Preserve Ambenonium Chloride in tight containers.

CATEGORY—Cholinergic.

USUAL DOSE—Initial, **5 mg.,** gradually increased as required up to **5** to **25 mg.** three or four times a day.

USUAL DOSE RANGE—**5 mg.** to **50 mg.**

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* Patented. See notice, page ii.

Ambenonium Chloride Tablets

Ambenonium Chloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{28}H_{42}Cl_4N_4O_2$.

Identification—The solution prepared from Ambenonium Chloride Tablets for measurement of absorbance in the *Assay* exhibits a maximum at 278 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Ambenonium Chloride Tablets is 15 minutes.

Content uniformity, *Method II,* page 799—Ambenonium Chloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer one finely powdered tablet to a 25-ml. volumetric flask, add 12 ml. of chloroform, and reflux on a steam bath for 15 minutes. Cool to room temperature, dilute to volume with chloroform, mix, and filter, discarding the first 5 ml. of filtrate. Dilute a portion of the subsequent filtrate with chloroform, if necessary, to provide a solution containing approximately 400 mcg. of ambenonium chloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Ambenonium Chloride Reference Standard, in the same medium at a concentration of about 400 mcg. per ml., in 1-cm. cells, at the maximum at about 278 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{28}H_{42}Cl_4N_4O_2$ in the Tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of ambenonium chloride in the tablet; D is the exact concentration, in mcg. per ml., of ambenonium chloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—

Standard preparation—Transfer about 25 mg. of NF Ambenonium Chloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add 0.1 N sulfuric acid to volume, and mix.

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 250-mm. tube to which is fused a 5-cm. length of 7-mm. tubing) with the aid of a tamping rod about 45 cm. in length and having a disk with a diameter about 1 mm. less than that of the tube. To 2 g. of purified siliceous earth in a 100-ml. beaker add 1 ml. of sodium carbonate solution (1 in 20), and mix until a uniform, fluffy mixture is obtained. Transfer to the tube, and tamp gently to compress the mixture to a uniform mass.

Assay preparation—Weigh and finely powder not less than 20 Ambenonium Chloride Tablets. Transfer to a 100-ml. beaker an accurately weighed portion of the powder, equivalent to about 12.5 mg. of ambenonium chloride, add 2 ml. of sodium carbonate solution (1 in 20), and allow to stand for about 10 minutes with occasional swirling. Add 3 g. of purified siliceous earth, mix as directed under *Chromatographic column*, and transfer quantitatively to the column. Scrub the beaker with 1 g. of purified siliceous earth and 3 drops of water, transfer the scrubbings to the column, and tamp gently. Cover the column with a pledget of glass wool. Wash the column with 75 ml. of water-saturated chloroform, followed by 75 ml. of water-saturated ether, and discard the washings. Elute the ambenonium chloride with 75 ml. of a 1 in 500 solution of bis(ethylhexyl)phosphoric acid in water-saturated ether, collecting the eluate in a 125-ml. separator. Extract the eluate with two 20-ml. portions of 0.1 N sulfuric acid, collecting the extracts in a 50-ml. volumetric flask. Dilute to volume with 0.1 N sulfuric acid, and mix.

Procedure—Concomitantly determine the absorbance of the *Standard preparation* and of the *Assay preparation*, in 1-cm. cells, at the maximum at about 271 mμ, with a suitable spectrophotometer, using 0.1 N sulfuric acid as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{28}H_{42}Cl_4N_4O_2$ in the portion of Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Ambenonium Chloride Tablets in tight containers.

Tablets available—Ambenonium Chloride Tablets usually available contain the following amounts of ambenonium chloride: 10 and 25 mg.

CATEGORY and DOSE—See Ambenonium Chloride.

Aminoacetic Acid

NH_2CH_2COOH

Glycine

$C_2H_5NO_2$ Mol. wt. 75.07

Aminoacetic Acid, dried at 105° for 2 hours, contains not less than 98.5 percent and not more than 101.5 percent of $C_2H_5NO_2$.

Description—Aminoacetic Acid occurs as a white, odorless, crystalline powder, having a sweetish taste. Its solution is acid to litmus.

Solubility—Aminoacetic Acid is freely soluble in water. It is very slightly soluble in alcohol and in ether.

Identification—

A: To 5 ml. of a solution of Aminoacetic Acid (1 in 10) add 5 drops of diluted hydrochloric acid and 5 drops of a solution of sodium nitrite (1 in 2): a vigorous evolution of a colorless gas is produced.

B: Add 1 ml. of ferric chloride T.S. to 2 ml. of a solution of Aminoacetic Acid (1 in 10): a red color is produced which disappears upon the addition of an excess of diluted hydrochloric acid and reappears upon the addition of an excess of stronger ammonia water.

C: To 2 ml. of a solution of Aminoacetic Acid (1 in 10) add 1 drop of liquefied phenol and 5 ml. of sodium hypochlorite T.S.: a blue color is produced.

Loss on drying, page 814—Dry Aminoacetic Acid at 105° for 2 hours: it loses not more than 0.2 percent of its weight.

Residue on ignition, page 858—Aminoacetic Acid yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—A solution of 1 g. of Aminoacetic Acid in water shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (70 parts per million).

Sulfate, page 784—A solution of 3 g. of Aminoacetic Acid in water shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (65 parts per million).

Heavy metals, page 806—Dissolve 1 g. of Aminoacetic Acid in 15 ml. of water, add 4 ml. of diluted acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Aminoacetic Acid is 20 parts per million.

Readily carbonizable substances, page 856—Dissolve 500 mg. of Aminoacetic Acid in 5 ml. of sulfuric acid T.S.: the solution is colorless.

Hydrolyzable substances—Boil 10 ml. of a solution of Aminoacetic Acid (1 in 10) for 1 minute, and set aside for 2 hours: the solution appears as clear and as mobile as 10 ml. of the same solution that has not been boiled.

Assay—Transfer about 150 mg. of Aminoacetic Acid, previously dried at 105° for 2 hours and accurately weighed, to a 250-ml. flask, dissolve it in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 7.507 mg. of $C_2H_5NO_2$.

Packaging and storage—Preserve Aminoacetic Acid in well-closed containers.

CATEGORY—Nutrient.

USUAL DOSE—**30 g.** daily, in divided doses.

APPLICATION—Irrigating solution as a 1.5 percent solution.

Aminoacetic Acid Sterile Solution

Aminoacetic Acid Sterile Solution is a sterile solution of aminoacetic acid in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_2H_5NO_2$.

Identification—Aminoacetic Acid Sterile Solution, when adjusted by evaporation or dilution as required to produce a concentration of about 100 mg. per ml. (1 in 10), responds to the *Identification tests* under *Aminoacetic Acid,* page 38.

pH, page 824—The pH of Aminoacetic Acid Sterile Solution is between 4.5 and 6.5.

Pyrogen—Aminoacetic Acid Sterile Solution, diluted if necessary with sodium chloride injection to a concentration of 1.5 percent, meets the requirements of the *Pyrogen Test,* page 851.

Other requirements—Aminoacetic Acid Sterile Solution meets the requirements under *Injections,* page 810, except that the container in which the Solution is packaged may be designed to empty rapidly and may exceed 1000 ml. in capacity.

Assay—Dilute an accurately measured volume of Aminoacetic Acid Sterile Solution, equivalent to about 150 mg. of aminoacetic acid, to 25 ml. with water, and add 10 ml. of formaldehyde T.S., previously adjusted to pH 9.0, and 5 drops of mixed indicator solution (prepared by dissolving 75 mg. of phenolphthalein and 25 mg. of thymol blue in a mixture of equal volumes of alcohol and water to make 100 ml.), and titrate with 0.1 *N* sodium hydroxide until the yellow color disappears and a faint violet color appears. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 7.507 mg. of $C_2H_5NO_2$.

Packaging and storage—Preserve Aminoacetic Acid Sterile Solution in single-dose containers, preferably of Type I or Type II glass.

Solutions available—Aminoacetic Acid Sterile Solution is usually available as a 1.5 percent solution in 1500, 2000, and 3000 ml., and as a 15 percent concentrate in 1000 ml.

CATEGORY and DOSE—See Aminoacetic Acid.

Aminocaproic Acid*

$NH_2CH_2(CH_2)_3CH_2COOH$

6-Aminohexanoic Acid

$C_6H_{13}NO_2$ Mol. wt. 131.18

Aminocaproic Acid contains not less than 98.5 percent and not more than 100.5 percent of $C_6H_{13}NO_2$, calculated on the anhydrous basis.

Description—Aminocaproic Acid occurs as a fine, white crystalline powder. It is odorless or nearly so. Its solutions are neutral to litmus. It melts at about 205°.

Solubility—Aminocaproic Acid is freely soluble in water, in acids, and in alkalies. It is slightly soluble in methanol and in alcohol, and is practically insoluble in chloroform and in ether.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Aminocaproic Acid, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Aminocaproic Acid Reference Standard, similarly measured.

Water, page 900—Determine the water content of Aminocaproic Acid by the titrimetric method: not more than 0.5 percent is found.

Residue on ignition, page 858—Aminocaproic Acid yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Aminocaproic Acid is 20 parts per million.

Assay—Transfer about 500 mg. of Aminocaproic Acid, accurately weighed, to a beaker, add about 100 ml. of glacial acetic acid, heat gently to effect solution, and cool. Add 10 drops of a 1 in 500 solution of crystal violet in chlorobenzene, and titrate with 0.1 *N* perchloric acid in dioxane to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 13.12 mg. of $C_6H_{13}NO_2$.

Packaging and storage—Preserve Aminocaproic Acid in tight containers.

CATEGORY—Hemostatic.

USUAL DOSE—Oral and intravenous, Initial, **5 g.** followed by **1** to **1.25 g.** every hour to maintain a plasma level of 13 mg. per 100 ml. No more than 30 g. per 24-hour period is recommended.

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* Patented. See notice, page ii.

Aminocaproic Acid Injection

Aminocaproic Acid Injection is a sterile solution of aminocaproic acid in water for injection. It contains not less than 95.0 percent and not more than 107.5 percent of the labeled amount of $C_6H_{13}NO_2$.

Identification—Mix 2 ml. of Aminocaproic Acid Injection, added dropwise, with 100 ml. of acetone, rapidly stirring the mixture with a glass rod to induce crystallization. Allow the mixture to stand for 15 minutes, and then filter through a medium-porosity sintered-glass filter. Wash the crystals with 25 ml. of acetone, apply vacuum to withdraw the solvent, then dry at 105° for 30 minutes, and cool. A potassium bromide dispersion prepared from the residue so obtained meets the requirements for *Infrared absorption* under *Aminocaproic Acid,* page 40.

pH, page 824—The pH of Aminocaproic Acid Injection is between 6.0 and 7.6.

Pyrogen—Aminocaproic Acid Injection meets the requirements of the *Pyrogen Test,* page 851, the test dose being 1 ml. per kg.

Other requirements—Aminocaproic Acid Injection meets the requirements under *Injections,* page 810.

Assay—Transfer an accurately measured portion of Aminocaproic Acid Injection, equivalent to 500 mg. of aminocaproic acid, to a beaker, add about 100 ml. of glacial acetic acid, mix, and proceed as directed in the *Assay* under *Aminocaproic Acid,* page 40, beginning with "Add 10 drops of a 1 in 500 solution of crystal violet in chlorobenzene. . . ."

Packaging and storage—Preserve Aminocaproic Acid Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injection available—Aminocaproic Acid Injection usually available contains the following amount of aminocaproic acid: 5 g. in 20 ml.

CATEGORY and DOSE—See Aminocaproic Acid.

Aminocaproic Acid Tablets

Aminocaproic Acid Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{13}NO_2$.

Identification—Triturate two Aminocaproic Acid Tablets with 10 ml. of water, and filter into 100 ml. of acetone. Swirl the mixture, and allow to stand for 15 minutes to complete crystallization. Filter through a medium porosity sintered-glass filter, and wash the crystals with 25 ml. of acetone. Apply vacuum to withdraw the solvent, then dry at 105° for 10 to 15 minutes, and cool: a potassium bromide dispersion prepared from the residue so obtained meets the requirements for *Infrared absorption* under *Aminocaproic Acid*, page 40.

Disintegration, page 878—The disintegration time limit for Aminocaproic Acid Tablets is 30 minutes.

Weight variation, page 901—Aminocaproic Acid Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Aminocaproic Acid Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg. of aminocaproic acid, to a beaker, add about 100 ml. of glacial acetic acid, heat gently to effect solution, and cool. Proceed as directed in the *Assay* under *Aminocaproic Acid,* page 40, beginning with "Add 10 drops of a 1 in 500 solution of crystal violet in chlorobenzene. . . ."

Packaging and storage—Preserve Aminocaproic Acid Tablets in tight containers.

Tablets available—Aminocaproic Acid Tablets usually available contain the following amount of aminocaproic acid: 500 mg.

CATEGORY and DOSE—See Aminocaproic Acid.

Aminosalicylate, Calcium, page 113
Aminosalicylate, Calcium, Capsules, page 115
Aminosalicylate, Calcium, Tablets, page 115

Strong Ammonia Solution

Strong Ammonia Solution is a solution of NH_3, containing not less than 27.0 percent and not more than 30.0 percent (w/w) of NH_3. Upon exposure to air it loses ammonia rapidly.

Caution: Use care in handling Strong Ammonia Solution because of the caustic nature of the Solution and the irritating properties of its vapor. Cool the container well before opening, and cover the closure with a cloth or similar material while opening. Do not taste Strong Ammonia Solution, and avoid inhalation of its vapor.

Description—Strong Ammonia Solution is a clear, colorless liquid, having an exceedingly pungent, characteristic odor. Its specific gravity is about 0.90.

Identification—Dense white fumes are produced if a glass rod wet with hydrochloric acid is held near the surface of Strong Ammonia Solution.

Nonvolatile residue—Evaporate a 10-ml. portion of Strong Ammonia Solution in a tared platinum or porcelain dish to dryness, and dry at 105° for 1 hour: not more than 5 mg. of residue remains (0.05 percent).

Heavy metals, page 806—Evaporate 5 ml. of Strong Ammonia Solution on a steam bath to dryness, add to the residue 1 ml. of diluted hydrochloric acid, and evaporate to dryness. Dissolve the residue in 2 ml. of diluted acetic acid, and add water to make 25 ml.: the heavy metals limit for Strong Ammonia Solution is 13 parts per million.

Readily oxidizable substances—To a mixture of 4 ml. of Strong Ammonia Solution and 6 ml. of water, add a slight excess of diluted sulfuric acid and 0.1 ml. of 0.1 *N* potassium permanganate: the pink color does not completely disappear within 10 minutes.

Assay—Transfer quickly a portion of Strong Ammonia Solution to a stoppered thick-walled container (a pressure bottle is suitable) to obtain a column height of about 20 cm., stopper, and cool the container and contents to 10° or lower. Weigh accurately a 125-ml. glass-stoppered conical flask containing 35.0 ml. of 1 *N* sulfuric acid. Insert a graduated 10-ml. measuring pipet into the cooled Strong

Ammonia Solution, allow the liquid to rise in the pipet without vacuum, remove the pipet, wipe off adhering liquid, and discard the first ml. of the Solution permitted to run from the pipet. Hold the pipet just above the surface of the 1 *N* sulfuric acid in the conical flask, and transfer about 2 ml. of the Solution into the flask. Stopper, mix, and reweigh to obtain the weight of the sample. Titrate the excess acid with 1 *N* sodium hydroxide, using 3 drops of methyl red T.S. as the indicator. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 1 *N* sulfuric acid is equivalent to 17.03 mg. of NH_3.

Packaging and storage—Preserve Strong Ammonia Solution in tight containers, preferably at a temperature not exceeding 25°.

Category—Solvent; source of ammonia.

Aromatic Ammonia Spirit

Aromatic Ammonia Spirit contains, in each 100 ml., not less than 1.7 g. and not more than 2.1 g. of total NH_3, and ammonium carbonate corresponding to not less than 3.5 g. and not more than 4.5 g. of $(NH_4)_2CO_3$.

Ammonium Carbonate, in translucent pieces	**34 g.**
Strong Ammonia Solution	**36 ml.**
Lemon Oil	**10 ml.**
Lavender Oil	**1 ml.**
Myristica Oil	**1 ml.**
Alcohol	**700 ml.**
Purified Water, a sufficient quantity	
To make	**1000 ml.**

Dissolve the ammonium carbonate in the strong ammonia solution and 195 ml. of purified water by gentle agitation, and allow the solution to stand for 12 hours. Dissolve the oils in the alcohol, contained in a graduated bottle or cylinder, and gradually add the ammonium carbonate solution and enough purified water to make the product measure 1000 ml. Set the mixture aside in a cool place for 24 hours, occasionally agitating it, and then filter, using a covered funnel.

Description—Aromatic Ammonia Spirit is a nearly colorless liquid when recently prepared, but gradually acquires a yellow color on standing. It has the taste of ammonia, has an aromatic and pungent odor, and is affected by light. Its specific gravity is about 0.90.

Assay for total NH_3—Pipet 10.0 ml. of Aromatic Ammonia Spirit into a 250-ml. conical flask containing about 50 ml. of water. Add 30.0 ml. of 0.5 *N* sulfuric acid, and boil until the solution becomes clear. Cool, add 3 drops of methyl red T.S., and titrate the excess acid with 0.5 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.5 *N* sulfuric acid is equivalent to 8.515 mg. of NH_3.

Assay for ammonium carbonate—Pipet 10.0 ml. of Aromatic Ammonia Spirit into a flask of about 300-ml. capacity. Add about 30 ml. of 0.5 *N* sodium hydroxide, and boil the mixture, replacing the water lost by evaporation, until the vapors no longer turn moistened red litmus paper blue. Cool, dilute with 100 ml. of cold, carbon dioxide-free water, add about 6 drops of phenolphthalein T.S., and then just enough 0.5 *N* sulfuric acid to discharge the color of the phenolphthalein. Then add 3 drops of methyl orange T.S., and titrate with 0.5 *N* sulfuric acid. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.5 *N* sulfuric acid consumed in the titration with methyl orange T.S. is equivalent to 48.04 mg. of $(NH_4)_2CO_3$.

Alcohol content, page 772—Aromatic Ammonia Spirit contains from 62 to 68 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Aromatic Ammonia Spirit in tight, light-resistant containers, preferably at a temperature not exceeding 30°.

Category—Respiratory stimulant.

Application—By inhalation of vapor as required.

Ammonium Carbonate

Ammonium Carbonate consists of ammonium bicarbonate (NH_4HCO_3) and ammonium carbamate (NH_2COONH_4) in varying proportions. It yields not less than 30.0 percent and not more than 34.0 percent of NH_3.

Description—Ammonium Carbonate occurs as a white powder or as hard, white or translucent masses, having a strong odor of ammonia, without empyreuma, and having a sharp, ammoniacal taste. Its solutions are alkaline to litmus. On exposure to air, it loses ammonia and carbon dioxide, becoming opaque, and is finally converted into friable porous lumps or a white powder of ammonium bicarbonate.

Solubility—Ammonium Carbonate is freely soluble in water, but is decomposed by hot water.

Identification—When heated, Ammonium Carbonate is volatilized without charring and the vapor is alkaline to moistened litmus paper. A solution of Ammonium Carbonate (1 in 20) effervesces with acids.

Residue on ignition, page 858—Ammonium Carbonate yields not more than 0.05 percent of residue on ignition.

Chloride, page 784—A 2-g. portion of Ammonium Carbonate shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (35 parts per million).

Sulfate, page 784—A 2-g. portion of Ammonium Carbonate shows no more sulfate than corresponds to 0.1 ml. of 0.02 *N* sulfuric acid (50 parts per million).

Heavy metals, page 806—Reduce Ammonium Carbonate to a coarse powder, and volatilize 2 g. of it on a steam bath. Add to the residue 1 ml. of diluted hydrochloric acid, and evaporate to dryness. Dissolve the residue in 2 ml. of diluted acetic acid, and add water to make 25 ml.: the heavy metals limit for Ammonium Carbonate is 10 parts per million.

Empyreumatic matter—Add a slight excess of nitric acid to a solution containing 1 g. of Ammonium Carbonate, and evaporate on a steam bath to dryness: a colorless, odorless residue is obtained.

Assay—Place in a weighing bottle about 10 ml. of water, tare the bottle and its contents, add about 2 g. of Ammonium Carbonate, and weigh accurately. Transfer the contents of the bottle to a 250-ml. flask, add 50.0 ml. of 1 *N* sulfuric acid, and, when solution has been effected, add 3 drops of methyl orange T.S., and titrate the excess acid with 1 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 1 *N* sulfuric acid is equivalent to 17.03 mg. of NH_3.

Packaging and storage—Preserve Ammonium Carbonate in tight, light-resistant containers, preferably at a temperature not exceeding 30°.

CATEGORY—Source of ammonia.

Amobarbital Elixir

Amobarbital Elixir contains, in each 100 ml., not less than 418 mg. and not more than 462 mg. of $C_{11}H_{18}N_2O_3$.

Amobarbital	**4.4**	**g.**
Methenamine	**4.4**	**g.**
Caramel	**11.25**	**ml.**
Propylene Glycol	**310**	**ml.**
Sodium Saccharin	**1**	**g.**
Orange Oil	**0.26**	**ml.**
Lemon Oil	**0.15**	**ml.**
Cinnamon Oil	**0.03**	**ml.**
Caraway Oil	**0.006**	**ml.**
Coriander Oil	**0.0018**	**ml.**
Anise Oil	**0.02**	**ml.**
Alcohol	**300**	**ml.**
Purified Water, a sufficient quantity,		
To make	**1000**	**ml.**

Dissolve the amobarbital, sodium saccharin, and oils in the alcohol. Add the propylene glycol, the methenamine, the caramel, and sufficient purified water to make the product measure 1000 ml. Mix well, allow the product to stand 24 hours, and filter until the elixir is clear.

Identification—The amobarbital obtained in the *Assay*, when recrystallized from hot alcohol and dried at 105° for 30 minutes, melts between 156° and 159°, page 814.

Assay—Transfer 25.0 ml. of Amobarbital Elixir to a separator and make it distinctly alkaline by the addition of sodium hydroxide T.S. Add 20 ml. of solvent hexane, shake the mixture for 5 minutes, allow it to separate, and draw off the water layer into a 125-ml. separator. Wash the solvent hexane portion with 10 ml. of water, add the washing to the water portion, and discard the solvent hexane. Acidify the water portion with hydrochloric acid, render it just alkaline to litmus by adding small portions of sodium bicarbonate, and extract with 5 successive 20-ml. portions of ether. Combine the ether extracts in a separator, wash thoroughly with three 10-ml. portions of water, and in turn wash these water extracts with 10 ml. of ether. Now discard the water portions and add the ether washings to the combined ether extracts in the separator. Filter the combined ether extracts through a dry filter paper into a tared 150-ml. beaker, wash the filter with ether, add the washings to the beaker, and evaporate to dryness on a steam bath. Dry the residue at 105° for 30 minutes. The weight of the amobarbital obtained is that of the $C_{11}H_{18}N_2O_3$ in the portion of the Elixir taken.

Alcohol content, page 772—Amobarbital Elixir contains from 26 to 32 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Amobarbital Elixir in tight containers.

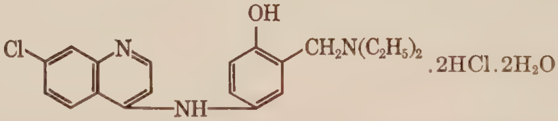
CATEGORY—Sedative.

USUAL DOSE—**5 ml.**

One usual dose contains 22 mg. of Amobarbital.

Amobarbital, Sodium, and Sodium Secobarbital Capsules, page 659

Amodiaquine Hydrochloride



4-[(7-Chloro-4-quinolyl)amino]-α-(diethylamino)-*o*-cresol Dihydrochloride

$C_{20}H_{22}ClN_3O.2HCl.2H_2O$ Mol. wt. 464.82

Amodiaquine Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{20}H_{22}ClN_3O.2HCl$, calculated on the anhydrous basis.

Description—Amodiaquine Hydrochloride occurs as a yellow, crystalline powder. It is odorless and has a bitter taste.

Solubility—Amodiaquine Hydrochloride is soluble in water. It is sparingly soluble in alcohol and is very slightly soluble in benzene, in chloroform, and in ether.

Completeness of solution, page 794—A solution of 200 mg. of Amodiaquine Hydrochloride in 10 ml. of water is clear.

Identification—

A: Amodiaquine Hydrochloride meets the requirements under *Identification—Organic Nitrogenous Bases*, page 810.

B: A solution of Amodiaquine Hydrochloride responds to the tests for *Chloride*, page 808.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Amodiaquine Hydrochloride, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Amodiaquine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Amodiaquine Hydrochloride in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Amodiaquine Hydrochloride Reference Standard, similarly measured.

Water, page 900—Determine the water content of Amodiaquine Hydrochloride by the titrimetric method: not less than 7 percent and not more than 9 percent is found.

Residue on ignition, page 858—Amodiaquine Hydrochloride yields not more than 0.2 percent of residue on ignition.

Assay—Accurately weigh about 300 mg. of undried Amodiaquine Hydrochloride, transfer to a 200-ml. volumetric flask, add 0.1 *N* hydrochloric acid to volume, and mix. Pipet 10.0 ml. of the solution into a 1000-ml. volumetric flask, add 0.1 *N* hydrochloric acid to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of undried NF Amodiaquine Hydrochloride Reference Standard, in the same medium, at a concentration of about 15 mcg. per ml. in 1-cm. cells, at the maximum at about 342 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{20}H_{22}ClN_3O.2HCl$ in the portion of Amodiaquine Hydrochloride taken by the formula $20C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., calculated on the anhydrous basis, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Amodiaquine Hydrochloride in tight containers.

Category—Antimalarial.

Usual dose—Suppressive, **520 mg.**, the equivalent of **400 mg.** of amodiaquine base, every 2 weeks. Therapeutic, **780 mg.** to **1.3 g.**, the equivalent of **600 mg.** to **1 g.** of amodiaquine base.

Amodiaquine Hydrochloride Tablets

Amodiaquine Hydrochloride Tablets contain an amount of $C_{20}H_{22}ClN_3O.2HCl.2H_2O$ (amodiaquine hydrochloride) equivalent to not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{20}H_{22}ClN_3O$ (amodiaquine base).

Identification—Digest a portion of finely powdered Amodiaquine Hydrochloride Tablets, equivalent to about 200 mg. of amodiaquine hydrochloride, with 50 ml. of water on a steam bath for 15 minutes. Cool, and filter the solution through hardened filter paper: the clear solution so obtained responds to the *Identification tests* under *Amodiaquine Hydrochloride*, page 44.

Ultraviolet absorption, page 866—The solution employed for measurement of absorbance in the *Assay* meets the requirements for *Ultraviolet absorption* under *Amodiaquine Hydrochloride*, page 44.

Disintegration, page 878—The disintegration time limit for Amodiaquine Hydrochloride Tablets is 30 minutes.

Weight variation, page 901—Amodiaquine Hydrochloride Tablets meet the requirements of the weight variation test for tablets.

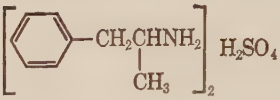
Assay—Weigh and finely powder not less than 20 Amodiaquine Hydrochloride Tablets. Weigh accurately a portion of the powder, equivalent to about 300 mg. of amodiaquine hydrochloride, and transfer to a 250-ml. beaker. Add about 100 ml. of 0.1 *N* hydrochloric acid, and heat on a steam bath for about 15 minutes with occasional stirring. Cool the mixture to room temperature, transfer to a 200-ml. volumetric flask, add 0.1 *N* hydrochloric acid to volume, and mix. Pipet 10.0 ml. of the clear supernatant liquid into a 125-ml. separator. Add about 10 ml. of 0.1 *N* hydrochloric acid, and wash with 20 ml. of chloroform, discarding the washings. Add 4.5 ml. of sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform. Extract the combined chloroform solutions with three 50-ml. portions of 0.1 *N* hydrochloric acid. Combine the acid extracts in a 200-ml. volumetric flask, add 0.1 *N* hydrochloric acid to volume, and mix. Pipet 20.0 ml. of this solution into a 100-ml. volumetric flask, add 0.1 *N* hydrochloric acid to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of undried NF Amodiaquine Hydrochloride Reference Standard, in the same medium, at a concentration of about 15 mcg. per ml., in 1-cm. cells, at the maximum at about 342 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{20}H_{22}ClN_3O.2HCl.2H_2O$ in the portion of the tablets taken by the formula $20C \times 1.084 \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., calculated on the anhydrous basis, A_U is the absorbance of the sample solution, A_S is the absorbance of the Reference Standard solution, and 1.084 is the conversion factor relating the anhydrous salt to the hydrated salt. The quantity determined, multiplied by 0.766 gives the equivalent quantity of $C_{20}H_{22}ClN_3O$.

Packaging and storage—Preserve Amodiaquine Hydrochloride Tablets in tight containers.

Tablets available—Amodiaquine Hydrochloride Tablets usually available contain the equivalent of the following amount of amodiaquine base: 200 mg.

Category and Dose—See Amodiaquine Hydrochloride.

Amphetamine Sulfate



(±)-α-Methylphenethylamine Sulfate (2:1)

$(C_9H_{13}N)_2 . H_2SO_4$ Mol. wt. 368.50

Amphetamine Sulfate, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 100.5 percent of $(C_9H_{13}N)_2 . H_2SO_4$.

Description—Amphetamine Sulfate occurs as a white, odorless, crystalline powder. It has a slightly bitter taste. Its solutions are acid to litmus, having a pH of 5 to 6.

Solubility—Amphetamine Sulfate is freely soluble in water, and is slightly soluble in alcohol. It is practically insoluble in ether.

Identification—

A: Dissolve about 100 mg. of Amphetamine Sulfate in 5 ml. of water, add 5 ml. of sodium hydroxide T.S., cool to about 10°, add 1 ml. of a mixture of 1 volume of benzoyl chloride and 2 volumes of absolute ether, stopper, and shake well for 3 minutes. Filter the precipitate, wash it with about 10 ml. of cold water, and recrystallize it from diluted alcohol: the crystals of the benzoyl derivative of amphetamine so obtained, after drying at 80° for 2 hours, melt between 131° and 135°, page 814.

B: A solution of Amphetamine Sulfate (1 in 10) responds to the tests for *Sulfate*, page 810.

Loss on drying, page 814—Dry Amphetamine Sulfate at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Amphetamine Sulfate yields not more than 0.2 percent of residue on ignition.

Dextroamphetamine—A solution of Amphetamine Sulfate (1 in 50) is optically inactive.

Assay—

Standard preparation—Prepare as directed for *Standard preparation* under *Amphetamine Assay*, page 776.

Assay preparation—Dissolve about 125 mg. of Amphetamine Sulfate, previously dried at 105° for 2 hours and accurately weighed, in 25 ml. of hydrochloric acid solution (1 in 100) in a 50-ml. volumetric flask, dilute to volume with the solvent, and mix. Pipet 2.0 ml. of the solution into a 100-ml. beaker containing 3 g. of purified siliceous earth, and mix until a fluffy mixture is obtained.

Procedure—Proceed as directed for *Procedure* under *Amphetamine Assay*, page 776. Calculate the quantity, in mg., of $(C_9H_{13}N)_2 . H_2SO_4$ in the portion of Amphetamine Sulfate taken by the formula $0.25C \times [(A_{U257} - A_{U280})/(A_{S257} - A_{S280})]$, in which C is the exact concentration, in mcg. per ml., of USP Dextroamphetamine Sulfate Reference Standard in the *Standard preparation*.

Packaging and storage—Preserve Amphetamine Sulfate in well-closed containers.

Category—Central stimulant.

Usual dose—Oral, **5 mg.** three times a day. Intramuscular and slow intravenous, for barbiturate poisoning, **10 mg.**

Usual dose range—Oral, **5** to **30 mg.** daily. Intravenous, **10** to **50 mg.**

Amphetamine Sulfate Injection

Amphetamine Sulfate Injection is a sterile solution of amphetamine sulfate in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $(C_9H_{13}N)_2 . H_2SO_4$.

Identification—Amphetamine Sulfate Injection responds to the *Identification tests* under *Amphetamine Sulfate*, page 46.

pH, page 824—The pH of Amphetamine Sulfate Injection is between 4.0 and 6.3.

Other requirements—Amphetamine Sulfate Injection meets the requirements under *Injections*, page 810.

Assay—*Standard preparation*—Prepare as directed for *Standard preparation* under *Amphetamine Assay*, page 776.

Assay preparation—Transfer an accurately measured volume of Amphetamine Sulfate Injection, equivalent to about 125 mg. of amphetamine sulfate, to a 50-ml. volumetric flask, dilute to volume with hydrochloric acid solution (1 in 100), and mix. Pipet 2.0 ml. of the solution into a 100-ml. beaker containing 3 g. of purified siliceous earth, and mix until a fluffy mixture is obtained.

Procedure—Proceed as directed for *Procedure* under *Amphetamine Assay,* page 776. Calculate the quantity, in mg., of $(C_9H_{13}N)_2 \cdot H_2SO_4$ in each ml. of the Injection taken by the formula $0.25 \times (C/V) \times [(A_{U257} - A_{U280})/(A_{S257} - A_{S280})]$, in which C is the exact concentration, in mcg. per ml., of USP Dextroamphetamine Sulfate Reference Standard in the *Standard preparation,* and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Amphetamine Sulfate Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injections available—Amphetamine Sulfate Injection usually available contains the following amounts of amphetamine sulfate: 20 mg. in 1 ml. and 600 mg. in 30 ml.

CATEGORY and DOSE—See Amphetamine Sulfate.

Amphetamine Sulfate Tables

Amphetamine Sulfate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $(C_9H_{13}N)_2 \cdot H_2SO_4$.

Identification—Macerate a quantity of powdered Amphetamine Sulfate Tablets, representing about 50 mg. of amphetamine sulfate, with 10 ml. of water for 30 minutes, and filter into a small flask. To the filtrate add 3 ml. of sodium hydroxide T.S. Cool to about 10° to 15°, add 1 ml. of a mixture of 1 volume of benzoyl chloride and 2 volumes of absolute ether, stopper, and shake well for 3 minutes. Filter the precipitate, wash it with about 15 ml. of cold water, and recrystallize it twice from diluted alcohol. The crystals of the benzoyl derivative of amphetamine so obtained, after drying at 80° for 2 hours, melt between 131° and 135°, page 814.

Disintegration, page 878—The disintegration time limit for Amphetamine Sulfate Tablets is 15 minutes.

Content uniformity, *Method I,* page 799—Amphetamine Sulfate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed for *Standard preparation* under *Amphetamine Assay,* page 776.

Assay preparation—Weigh and finely powder not less than 20 Amphetamine Sulfate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg. of amphetamine sulfate, to a 100-ml. beaker, add 2 ml. of hydrochloric acid solution (1 in 100), swirl gently to wet the powder thoroughly, warm on a steam bath for about 1 minute, with occasional gentle swirling, and cool. Add 3 g. of purified siliceous earth, and mix until a fluffy mixture is obtained.

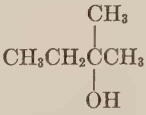
Procedure—Proceed as directed for *Procedure* under *Amphetamine Assay,* page 776. Calculate the quantity in mg., of $(C_9H_{13}N)_2 \cdot H_2SO_4$ in the portion of the Tablets taken by the formula $0.01C \times [(A_{U257} - A_{U280})/(A_{S257} - A_{S280})]$, in which C is the exact concentration, in mcg. per ml., of USP Dextroamphetamine Sulfate Reference Standard in the *Standard preparation.*

Packaging and storage—Preserve Amphetamine Sulfate Tablets in well-closed containers.

Tablets available—Amphetamine Sulfate Tablets usually available contain the following amounts of amphetamine sulfate: 5 and 10 mg.

CATEGORY and DOSE—See Amphetamine Sulfate.

Amylene Hydrate



$$\begin{array}{c} CH_3 \\ | \\ CH_3CH_2CCH_3 \\ | \\ OH \end{array}$$

tert-Pentyl Alcohol

$C_5H_{12}O$ Mol. wt. 88.15

Description—Amylene Hydrate occurs as a clear, colorless liquid, having a camphoraceous odor. Its solutions are neutral to litmus.

Solubility—Amylene Hydrate is freely soluble in water. It is miscible with alcohol, with chloroform, with ether, and with glycerin.

Identification—

A: Mix 2 ml. of Amylene Hydrate with 15 ml. of water, 5 ml. of sulfuric acid, and 10 g. of potassium dichromate, heat the mixture under a reflux condenser for 2 hours, then distil, collecting and reserving the first 2 ml. of the distillate. Continue the distillation until most of the water has distilled over, make this distillate alkaline with sodium hydroxide T.S., add diluted sulfuric acid dropwise until the solution is neutral to litmus paper, and carefully evaporate to dryness: the residue responds to the tests for *Acetate*, page 807.

B: To 1 ml. of the reserved distillate, obtained in *Identification test A*, add 5 drops of sodium nitroferricyanide T.S., 2 ml. of sodium hydroxide T.S., then a slight excess of acetic acid: a deep red liquid, which develops a violet tint when diluted with several volumes of water, is produced.

C: To 10 ml. of a solution of Amylene Hydrate (1 in 10) quickly add 5 ml. of a 1 in 100 solution of vanillin in sulfuric acid: a violet-red color is produced.

Specific gravity, page 866—The specific gravity of Amylene Hydrate is not less than 0.803 and not more than 0.807.

Distilling range, *Method I,* page 782—Amylene Hydrate distils completely between 97° and 103°.

Water—To 10 ml. of Amylene Hydrate add 1 g. of anhydrous cupric sulfate, and shake well: the cupric sulfate does not become blue.

Nonvolatile residue—Evaporate 10 ml. of Amylene Hydrate in a tared porcelain dish on a steam bath to a volume of about 1 ml., and allow it to evaporate spontaneously to dryness while protected from dust: the residue, if any, is colorless, and, when dried at 105° for 1 hour, weighs not more than 2 mg. (0.02 percent).

Heavy metals, page 806—Evaporate 2.5 ml. (2 g.) of Amylene Hydrate on a steam bath to dryness, warm the residue gently with 1 ml. of 0.1 *N* hydrochloric acid, add water to make 25 ml., and filter if necessary: the heavy metals limit for Amylene Hydrate is 5 parts per million.

Readily oxidizable substances—To 10 ml. of a solution of Amylene Hydrate (1 in 20) add 0.1 ml. of 0.1 *N* potassium permanganate: the pink color does not completely disappear within 10 minutes.

Aldehyde—To 10 ml. of a solution of Amylene Hydrate (1 in 20) add 1 ml. of silver-ammonium nitrate T.S., and heat the mixture on a water bath at 60° for 10 minutes: no darkening occurs.

Packaging and storage—Preserve Amylene Hydrate in tight containers.

CATEGORY—Solvent.

Amyl Nitrite

$(CH_3)_2CHCH_2CH_2ONO$

Isopentyl Nitrite

$C_5H_{11}NO_2$ Mol. wt. 117.15

Amyl Nitrite contains not less than 95.0 percent and not more than 105.0 percent of $C_5H_{11}NO_2$.

Caution: Amyl Nitrite is very flammable. Do not use where it may be ignited.

Description—Amyl Nitrite is a clear, yellowish liquid, having a peculiar, ethereal, fruity odor. It is volatile even at low temperatures and is flammable.

Solubility—Amyl Nitrite is practically insoluble in water, but is miscible with alcohol and with ether.

Identification—

A: To a mixture of 2 drops of Amyl Nitrite and 2 drops of water add 2 ml. of sulfuric acid, and then dilute with water: the odor of amyl valerate is perceptible.

B: To a few drops of Amyl Nitrite add a mixture of 1 ml. of ferrous sulfate T.S. and 5 ml. of diluted hydrochloric acid: a greenish brown color is produced.

Specific gravity, page 866—The specific gravity of Amyl Nitrite is not less than 0.871 and not more than 0.875.

Acidity—To 5 ml. of Amyl Nitrite, in a glass-stoppered cylinder, add a mixture of 1 ml. of 1 *N* sodium hydroxide, 10 ml. of water, and 1 drop of phenolphthalein T.S., and invert the cylinder 3 times: the red tint of the water layer is still perceptible.

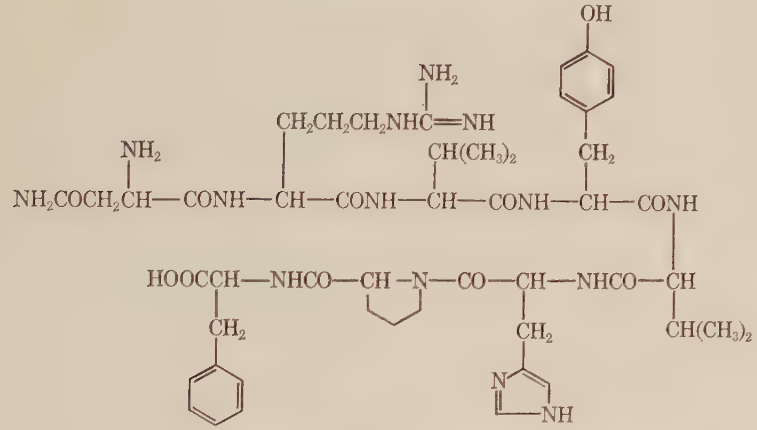
Assay—Shake about 3 ml. of Amyl Nitrite with 500 mg. of anhydrous potassium carbonate, decant carefully, transfer to a 100-ml. volumetric flask tared with about 20 ml. of alcohol, and weigh accurately. Add alcohol to volume, and mix. Fill a nitrometer with a saturated solution of sodium chloride, pipet into the funnel top 10.0 ml. of the alcohol solution, and, after drawing this into the measuring tube of the nitrometer without the admission of air, follow it with 5 ml. of alcohol as a rinse, then with 10 ml. of potassium iodide T.S., and afterwards with 5 ml. of diluted sulfuric acid, introducing each reagent separately into the measuring tube. When the volume of gas has become constant (in about 30 to 60 minutes), note the amount collected, the temperature at the nitrometer, and the barometric pressure. Multiply the volume of gas in ml. by 4.8, and divide the product by the weight of Amyl Nitrite taken. At 25° and 760 mm. pressure, the quotient represents the percentage of $C_5H_{11}NO_2$ in the liquid. The temperature correction is $^{1}/_{298}$ of the total percentage just found for each degree, added if the temperature is below 25°, and subtracted if it is above 25°. The barometric correction is $^{1}/_{760}$ of the total percentage just found for each mm., added if it is above 760 mm., and subtracted if it is below 760 mm.

Packaging and storage—Preserve Amyl Nitrite in tight containers. Containers for the administration of Amyl Nitrite by inhalation are wrapped loosely in gauze or other suitable material.

Category—Vasodilator.

Usual dose—Inhalation, **0.3 ml.** as required.

Angiotensin Amide



1-L-Asparagine-5-L-valineangiotensin II

$C_{49}H_{70}N_{14}O_{11}$ Mol. wt. 1031.19

Angiotensin Amide contains not less than 77.0 percent of $C_{49}H_{70}N_{14}O_{11}$.

Description—Angiotensin Amide occurs as a white to slightly off-white, odorless, amorphous powder.

Solubility—Angiotensin Amide is soluble in water, slightly soluble in methanol, and insoluble in ether and in chloroform.

Identification—Line the inside of a chromatographic chamber suitable for descending chromatography (see page 786) with filter paper. Fill the solvent trough with a mixture prepared by diluting 70 ml. of secondary butyl alcohol to 100 ml. with dilute ammonia T.S. (1 in 3) to serve as the mobile phase, and also place a sufficient amount of the same mixture on the bottom of the chamber to permit the liner to be in contact with it. Allow the chamber to equilibrate overnight. Prepare a 10 × 45-cm. strip of Whatman No. 1 or equivalent filter paper, draw a line across the narrow dimension about 6 cm. from one end, and mark two points for application of solutions along this line about 2.5 cm. from each edge of the paper. With a micropipet spot 10 μl. of an aqueous solution containing 5 mg. of Angiotensin Amide in each ml., and similarly spot in another position 10 μl. of an aqueous solution containing 5 mg. per ml. of NF Angiotensin Amide Reference Standard. Suspend the strip in the chamber, and allow to develop for 16 hours. Remove the strip, mark the solvent front, and dry the strip in air. Spray the strip with a visualizing solution prepared as follows: immediately before use, dissolve 100 mg. of sulfanilic acid in a mixture of 1 ml. of hydrochloric acid and 9 ml. of water, add 10 ml. of sodium nitrite solution (1 in 20), allow to stand for several minutes, and then add 20 ml. of sodium carbonate T.S.: The R_f value of the main spot from the sample solution corresponds to that obtained from the Reference Standard solution.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Angiotensin Amide in 2 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Angiotensin Amide Reference Standard, similarly measured.

Specific rotation, page 822—Determine the apparent specific rotation of a solution of Angiotensin Amide in 0.5 *N* hydrochloric acid containing 10 mg. of Angiotensin Amide in each ml., at 20°, in a 1-decimeter tube: the corrected specific rotation, calculated by dividing the apparent specific rotation by the percent purity determined as directed in the *Assay,* is between $-68°$ and $-76°$.

Assay—

Tyrosine stock solution—Transfer about 150 mg. of NF Tyrosine Reference Standard, previously dried to constant weight at 110° and accurately weighed, to a 50-ml. volumetric flask, add sodium hydroxide T.S. to volume, and mix.

Acidic standard preparation—Transfer 10.0 ml. of *Tyrosine stock solution* to a 100-ml. volumetric flask, dilute to volume with 2 *N* hydrochloric acid, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with 2 *N* hydrochloric acid, and mix.

Alkaline standard preparation—Transfer 10.0 ml. of *Tyrosine stock solution* to a 100-ml. volumetric flask, dilute to volume with 2 *N* sodium hydroxide, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with 2 *N* sodium hydroxide, and mix.

Assay stock solution—Transfer about 100 mg. of Angiotensin Amide, accurately weighed, to a 25-ml. volumetric flask, add water to volume, and mix.

Acidic assay preparation—Transfer 5.0 ml. of *Assay stock solution* to a 100-ml. volumetric flask, dilute to volume with 2 *N* hydrochloric acid, and mix.

Alkaline assay preparation—Transfer 5.0 ml. of *Assay stock solution* to a 100-ml. volumetric flask, dilute to volume with 2 *N* sodium hydroxide, and mix.

Procedure—Concomitantly determine the absorbances of the *Acidic standard preparation,* the *Acidic assay preparation,* the *Alkaline standard preparation,* and the *Alkaline assay preparation,* in 1-cm. cells, at the maximum at about 294 mμ, with a suitable spectrophotometer, using 2 *N* hydrochloric acid as the blank for the acidic preparations and 2 *N* sodium hydroxide as the blank for the alkaline preparations. Calculate the quantity, in mg., of $C_{49}H_{70}N_{14}O_{11}$ in the Angiotensin Amide taken by the formula $0.5C \times 5.691 \times (A_{U1} - A_{U2})/(A_{S1} - A_{S2})$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparations,* 5.691 is the ratio of the molecular weight of angiotensin amide to tyrosine, A_{U1} is the absorbance of the *Alkaline assay preparation,* A_{U2} is the absorbance of the *Acidic assay preparation,* A_{S1} is the absorbance of the *Alkaline standard preparation,* and A_{S2} is the absorbance of the *Acidic standard preparation.*

Packaging and storage—Preserve Angiotensin Amide in tight, light-resistant containers.

Category—Vasopressor.

Usual Dose Range—Intravenous infusion, **3** to **10 mcg.** per minute as determined by blood pressure response.

Angiotensin Amide for Injection

Angiotensin Amide for Injection is a sterile, dry mixture of angiotensin amide with suitable diluents. It contains not less than 92.0 percent and not more than 108.0 percent of the labeled amount of $C_{49}H_{70}N_{14}O_{11}$.

Identification—Transfer to a 10-ml. volumetric flask a quantity of Angiotensin Amide for Injection, equivalent to about 2.5 mg. of angiotensin amide, add water to volume, and mix. Dilute 2.0 ml. of this solution to 10.0 ml. with 2 *N* hydrochloric acid, and dilute another 2.0-ml. portion of the solution to 10.0 ml. with 2 *N* sodium hydroxide. The ultraviolet absorption spectra of the solutions, respectively, exhibit maxima and minima at the same wavelengths as those of similar solutions prepared from NF Angiotensin Amide Reference Standard, similarly measured.

Pyrogen—Angiotensin Amide for Injection meets the requirements of the *Pyrogen Test,* page 851, the test dose being 1.0 ml. per kg. of a solution containing 500 mcg. of angiotensin amide in each ml.

pH, page 824—The pH of a solution of Angiotensin Amide for Injection containing about 500 mcg. of angiotensin amide in each ml. is between 5.0 and 6.5.

Content uniformity, *Method I,* page 798—Angiotensin Amide for Injection meets the requirements of the content uniformity test for sterile solids.

Water—

Standard preparation—Transfer 2.0 ml. of water to a 200-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Determine the water content of this solution by the titrimetric method, page 900.

Test preparation—If the sample is in an ampul, open the ampul, quickly introduce and mix 100 µl. of methanol, using a 100-µl. syringe, and use immediately as directed in the *Procedure*. If the sample is in a vial, introduce 500 µl. of methanol through the stopper of the unopened vial, using a suitable syringe, and mix.

Procedure—Inject 10 µl. of methanol into a suitable gas-liquid chromatograph (see page 787), equipped with a 2-meter by 6-mm. (outside diameter) column packed with fluorinated ethylene-propylene resin on 40 to 60-mesh nonoxynol 9; the column is maintained at a temperature of 80°, and helium is used as the carrier gas at a flow rate of about 60 ml. per minute. Record the chromatogram. Similarly, inject 10 µl. each of the *Standard preparation* and of the *Test preparation*, and record the respective chromatograms. Calculate the quantity, in mg., of water in the sample by the formula $W \times V \times (A_U - A_B)/(A_S)$, in which W is the weight, in mg., of water per ml. of the *Standard preparation*, V is the volume, in ml., of methanol used in preparing the *Test preparation*, A_U is the area of the water peak from the *Test preparation*, A_B is the area of the water peak from the methanol blank, and A_S is the area of the water peak from the *Standard preparation:* not more than 1 percent of water is found.

Other requirements — Angiotensin Amide for Injection meets the requirements for *Sterility Tests*, page 874, and for *Labeling* under *Injections*, page 810.

Assay—

Acidic standard preparation and *Alkaline standard preparation*—Prepare as directed in the *Assay* under *Angiotensin Amide*, page 49.

Acidic assay preparation—Transfer an accurately weighed quantity of Angiotensin Amide for Injection, equivalent to about 2 mg. of angiotensin amide, to a 10-ml. volumetric flask, add 2 *N* hydrochloric acid to volume, and mix.

Alkaline assay preparation—Transfer an accurately weighed quantity of Angiotensin Amide for Injection, equivalent to about 2 mg. of angiotensin amide, to a 10-ml. volumetric flask, add 2 *N* sodium hydroxide to volume, and mix.

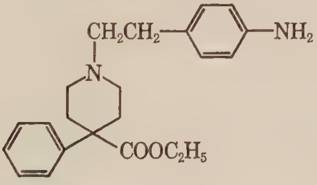
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Angiotensin Amide*, page 49. Calculate the quantity, in mg., of $C_{49}H_{70}N_{14}O_{11}$ in the sample taken by the formula $0.01C \times 5.691 \times (A_{U1} - A_{U2})/(A_{S1} - A_{S2})$.

Packaging and storage—Preserve Angiotensin Amide for Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Sizes available—Angiotensin Amide for Injection usually available contains the following amounts of angiotensin amide: 500 mcg. and 2.5 mg.

CATEGORY and DOSE—See Angiotensin Amide.

Anileridine*



Ethyl 1-(*p*-Aminophenethyl)-4-phenylisonipecotate

$C_{22}H_{28}N_2O_2$ Mol. wt. 352.48

Anileridine contains not less than 98.5 percent and not more than 101.0 percent of $C_{22}H_{28}N_2O_2$, calculated on the anhydrous basis.

Description—Anileridine occurs as a white to yellowish white, odorless to practically odorless crystalline powder. It oxidizes and darkens in air and on exposure to light. It exhibits polymorphism, and of two crystalline forms observed, one melts at about 80° and the other at about 89°.

Solubility—Anileridine is freely soluble in alcohol and in chloroform. It is very slightly soluble in water. It is soluble in ether although it may show turbidity.

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* Patented. See notice, page ii.

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Identification—To 5 ml. of a solution of Anileridine in 0.1 *N* hydrochloric acid (1 in 5000) add 2 ml. of a solution of *p*-dimethylaminobenzaldehyde in alcohol (1 in 100): a yellow color develops immediately.

Ultraviolet absorption, page 866—Dissolve 40 mg. of Anileridine in 2.3 ml. of 0.1 *N* hydrochloric acid in a 100-ml. volumetric flask, dilute to volume with water, and mix (*Stock solution*). Transfer 4.0 ml. of this solution into a 100-ml. volumetric flask, and add 25 ml. of pH 7.0 *Buffer solution.* (Prepare the *Buffer solution* by dissolving 22.73 g. of anhydrous dibasic sodium phosphate and 14.52 g. of monobasic potassium phosphate in sufficient water to make 1000.0 ml. Dilute 25 ml. of the buffer to 100 ml.: the pH, determined potentiometrically, should be 7.0 ± 0.05.) Dilute to volume with water, and mix (*Solution A*). Transfer 20.0 ml. of the *Stock solution* to a 100-ml. volumetric flask, add 25 ml. of the pH 7.0 *Buffer solution,* dilute to volume with water, and mix (*Solution B*). The ultraviolet absorption spectrum of *Solution A* exhibits a maximum at 234 ± 1 mμ, and the ultraviolet absorption spectrum of *Solution B* exhibits a maximum at 285 ± 2 mμ. The ratio $5A_{234}/A_{285}$ is about 8.8.

Water, page 900—Determine the water content of Anileridine by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Anileridine yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—Dissolve 180 mg. of Anileridine in a mixture of 1 ml. of nitric acid and 40 ml. of water: the solution shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (0.04 percent).

Assay—Dissolve about 350 mg. of Anileridine, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 17.62 mg. of $C_{22}H_{28}N_2O_2$.

Packaging and storage—Preserve Anileridine in tight, light-resistant containers.

CATEGORY—Analgesic (narcotic).

USUAL DOSE—Subcutaneous or intramuscular, **25** to **50 mg.** of Anileridine, present as the phosphate, repeated every 6 hours, if necessary.

USUAL DOSE RANGE—**25** to **75 mg.**

Anileridine Injection

Anileridine Injection is a sterile solution of anileridine in water for injection, prepared with the aid of phosphoric acid. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{22}H_{28}N_2O_2$, present as the phosphate.

Identification—

A: Dilute a volume of Anileridine Injection, equivalent to about 1.25 mg. of anileridine, to 5 ml. with water and add 2 ml. of a solution of *p*-dimethylaminobenzaldehyde in alcohol (1 in 100): a yellow color develops immediately.

B: Anileridine Injection, diluted with water to a concentration of about 25 mg. of anileridine in 1000 ml., exhibits absorbance maxima at 234 ± 1 mμ and 285 ± 2 mμ.

pH, page 824—The pH of Anileridine Injection is between 4.5 and 5.0.

Other requirements—Anileridine Injection meets the requirements under *Injections,* page 810.

Assay—

Standard preparation—Transfer to a 500-ml. volumetric flask about 120 mg. of NF Anileridine Hydrochloride, previously dried for 2 hours at 100° at a pressure not exceeding 5 mm. of mercury and accurately weighed, add 0.1 *N* hydrochloric acid to volume, and mix. (Each mg. of anileridine hydrochloride is equivalent to 0.8286 mg. of anileridine base.) Prepare a fresh *Standard preparation* on the day of the assay.

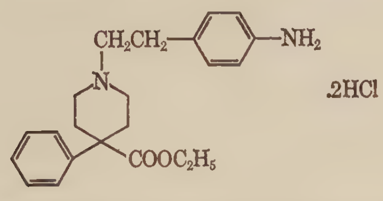
Assay preparation—Transfer to a 500-ml. volumetric flask an accurately measured volume of Anileridine Injection, equivalent to about 100 mg. of anileridine base, dilute to volume with 0.1 *N* hydrochloric acid, and mix.

Procedure—Pipet 5.0 ml. of the *Standard preparation,* of the *Assay preparation,* and of 0.1 *N* hydrochloric acid into separate 200-ml. volumetric flasks. To each flask add 25 ml. of water, 5 ml. of 1 *N* hydrochloric acid, and 5 ml. of sodium nitrite solution (1 in 1000), and mix. Allow to stand for 2 minutes, then add to each flask 5 ml. of ammonium sulfamate solution (1 in 200), and mix. Allow to stand for 3 minutes, then add 5 ml. of *N*-1-naphthylethylenediamine dihydrochloride solution (1 in 1000), and mix. Allow to stand for 1 hour, dilute to volume with water, and mix. Determine the absorbances of the solutions obtained from the *Standard preparation* and the *Assay preparation* at the maximum at about 560 mμ in a suitable spectrophotometer, using the reagent blank to set the instrument. Calculate the quantity, in mg., of $C_{22}H_{28}N_2O_2$ in each ml. of the Injection taken, by the formula $0.5 \times (C/V) \times 0.8286 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Anileridine Hydrochloride in the *Standard preparation*, V is the volume, in ml., of the Injection taken, A_U and A_S are the absorbances of the solutions obtained from the *Assay preparation* and the *Standard preparation*, respectively, and 0.8286 is the factor converting anileridine hydrochloride to anileridine.

Injections available—Anileridine Injection usually available contains the following amounts of anileridine: 25 mg. in 1 ml., 50 mg. in 2 ml., and 750 mg. in 30 ml.

CATEGORY and DOSE—See Anileridine.

Anileridine Hydrochloride*



Ethyl 1-(*p*-Aminophenethyl)-4-phenylisonipecotate Dihydrochloride

$C_{22}H_{28}N_2O_2 . 2HCl$ Mol. wt. 425.40

Anileridine Hydrochloride contains not less than 96.0 percent and not more than 102.0 percent of $C_{22}H_{28}N_2O_2 . 2HCl$, calculated on the dried basis.

Description—Anileridine Hydrochloride occurs as a white or nearly white, crystalline, odorless powder. It is stable in air. It melts at about 270° with decomposition.

Solubility—Anileridine Hydrochloride is freely soluble in water. It is sparingly soluble in alcohol, and practically insoluble in ether and in chloroform.

Identification—

A: To 5 ml. of a solution of Anileridine Hydrochloride (1 in 5000) add 2 ml. of a *p*-dimethylaminobenzaldehyde solution in alcohol (1 in 100): a yellow color develops immediately.

B: A solution of Anileridine Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 784.

Ultraviolet absorption, page 866—Dissolve 50 mg. of Anileridine Hydrochloride in water in a 100-ml. volumetric flask, dilute to volume, and mix (*Stock solution*). Transfer 4.0 ml. of this solution to a 100-ml. volumetric flask, and add 25 ml. of a pH 7.0 *Buffer solution*. (Prepare the *Buffer solution* by dissolving 22.73 g. of anhydrous dibasic sodium phosphate and 14.52 g. of monobasic potassium phosphate in sufficient water to make 1000.0 ml. Dilute 25 ml. of the buffer to 100 ml.: the pH, determined potentiometrically, should be 7.0 ± 0.05.) Dilute to volume with water, and mix (*Solution A*). Transfer 20.0 ml. of the *Stock solution* to a 100-ml. volumetric flask, add 25 ml. of the pH 7.0 *Buffer solution*, dilute to volume with water, and mix (*Solution B*). The ultraviolet absorption spectrum of *Solution A* exhibits a maximum at 234 ± 1 mμ, and the ultraviolet absorption spectrum of *Solution B* exhibits a maximum at 285 ± 2 mμ. The ratio $5A_{234}/A_{285}$ is about 8.8.

pH, page 824—The pH of a solution of Anileridine Hydrochloride (1 in 20) is between 2.5 and 3.0.

Loss on drying, page 814—Dry Anileridine Hydrochloride at 100° in vacuum, maintaining the pressure below 5 mm. of mercury, for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Anileridine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Chloride content—Dissolve about 200 mg. of Anileridine Hydrochloride, accurately weighed, in 50 ml. of water in a glass-stoppered flask. Add 25.0 ml. of 0.1 *N* silver nitrate, then add 5 ml. of diluted nitric acid and 5 ml. of nitrobenzene, shake vigorously, add 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 3.545 mg. of Cl. Not less than 16 percent and not more than 17.2 percent of Cl is found.

Assay—Dissolve about 200 mg. of Anileridine Hydrochloride, accurately weighed, in 10 ml. of glacial acetic acid by heating on a steam bath. Cool immediately in a cold water bath, add 5 ml. of mercuric acetate T.S., 20 ml. of acetone, and 0.5 ml. of indicator solution (70)mg.

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* Patented. See notice, page ii.

α-naphtholbenzein, 10 mg. crystal violet, and 40 mg. quinaldine red in 100 ml. of glacial acetic acid), and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a gray-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 21.27 mg. of $C_{22}H_{28}N_2O_2.2HCl$.

Packaging and storage—Preserve Anileridine Hydrochloride in tight, light-resistant containers.

CATEGORY—Analgesic (narcotic).

USUAL DOSE—**25 mg.** of anileridine, present as the dihydrochloride, repeated every 6 hours if necessary.

USUAL DOSE RANGE—**25** to **50 mg.**

Anileridine Hydrochloride Tablets

Anileridine Hydrochloride Tablets contain an amount of $C_{22}H_{28}N_2O_2.2HCl$ (anileridine hydrochloride) equivalent to not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{22}H_{28}N_2O_2$ (anileridine).

Identification—

A: Place a quantity of finely powdered Anileridine Hydrochloride Tablets, equivalent to about 50 mg. of anileridine hydrochloride, in a 250-ml. volumetric flask, add 100 ml. of water, and heat on a steam bath. Cool, dilute to volume with water, mix, and filter. Five ml. of the filtrate responds to *Identification test A* under *Anileridine Hydrochloride*, page 53.

B: Transfer to a 100-ml. volumetric flask a quantity of finely powdered Anileridine Hydrochloride Tablets, equivalent to about 50 mg. of anileridine hydrochloride. Add about 30 ml. of water, and heat on a steam bath. Cool, dilute to volume with water, mix, and filter (*Stock solution*). The filtrate responds to the *Ultraviolet absorption test* under *Anileridine Hydrochloride*, page 53, beginning with "Transfer 4.0 ml. of this solution. . . ."

Disintegration, page 878—The disintegration time limit for Anileridine Hydrochloride Tablets is 25 minutes.

Content uniformity, *Method I*, page 799—Anileridine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Transfer to a 500-ml. volumetric flask about 120 mg. of NF Anileridine Hydrochloride, previously dried for 2 hours at 100° at a pressure not exceeding 5 mm. of mercury and accurately weighed, add 0.1 *N* hydrochloric acid to volume, and mix. (Each mg. of anileridine hydrochloride is equivalent to 0.8286 mg. of anileridine base.) Prepare a fresh *Standard preparation* on the day of the assay.

Assay preparation—Weigh and finely powder not less than 20 Anileridine Hydrochloride Tablets. Weigh accurately a portion of the powder, equivalent to about 50 mg. of anileridine base, and transfer to a 250-ml. volumetric flask. Add 25 ml. of 1 *N* hydrochloric acid and 100 ml. of water, and heat on a water bath. Cool, dilute to volume with water, and mix. Filter the solution, discarding the first 25 ml. of the filtrate.

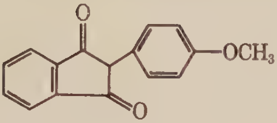
Procedure—Pipet 5.0 ml. of the *Standard preparation*, of the *Assay preparation*, and of 0.1 *N* hydrochloric acid into separate 200-ml. volumetric flasks. To each flask add 25 ml. of water, 5 ml. of 1 *N* hydrochloric acid, and 5 ml. of sodium nitrite solution (1 in 1000), and mix. Allow to stand for 2 minutes, then add to each flask 5 ml. of ammonium sulfamate solution (1 in 200), and mix. Allow to stand for 3 minutes, then add 5 ml. of *N*-1-naphthylethylenediamine dihydrochloride solution (1 in 1000), and mix. Allow to stand for 1 hour, dilute to volume with water, and mix. Concomitantly determine the absorbance of the solutions obtained from the *Standard preparation* and the *Assay preparation*, in 1-cm. cells, at 560 mμ with a suitable spectrophotometer, using the reagent blank to set the instrument. Calculate the quantity, in mg., of $C_{22}H_{28}N_2O_2$, in the portion of the Tablets taken, by the formula $0.25C \times 0.8286 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Anileridine Hydrochloride in the *Standard preparation*, A_U and A_S are the absorbances of the solutions obtained from the *Assay preparation* and the *Standard preparation*, respectively, and 0.8286 is the factor converting anileridine hydrochloride to anileridine.

Packaging and storage—Preserve Anileridine Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Anileridine Hydrochloride Tablets usually available contain the following amount of anileridine: 25 mg.

CATEGORY and DOSE—See Anileridine Hydrochloride.

Anisindione*



2-(*p*-Methoxyphenyl)-1,3-indandione

$C_{16}H_{12}O_3$ Mol. wt. 252.27

Anisindione contains not less than 97.0 percent and not more than 103.0 percent of $C_{16}H_{12}O_3$, calculated on the dried basis.

Description—Anisindione occurs as a white to creamy white powder. It is odorless or has a slightly sweet odor.

Solubility—Anisindione is practically insoluble in water, sparingly soluble in sodium hydroxide T.S., and slightly soluble in ether and in methanol. It is very slightly soluble in hydrochloric acid.

Identification—Dissolve about 10 mg. of Anisindione in 20 ml. of alcohol, and add a few drops of 0.1 *N* sodium hydroxide: a deep red color is produced.

Melting range, page 814—Anisindione melts between 152° and 158°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Anisindione, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Anisindione Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Anisindione in 0.1 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Anisindione Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 279 mμ, do not differ by more than 2.5 percent.

Loss on drying, page 814—Dry Anisindione at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Anisindione yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 500 mg. of Anisindione, accurately weighed, in 100 ml. of acetone, and titrate rapidly with 0.1 *N* tetrabutylammonium hydroxide, determining the end-point potentiometrically and delivering the titrant from a buret equipped with a carbon dioxide absorption trap. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* tetrabutylammonium hydroxide is equivalent to 25.23 mg. of $C_{16}H_{12}O_3$.

Packaging and storage—Preserve Anisindione in tight containers.

CATEGORY—Anticoagulant.

USUAL DOSE—Initial, **300 mg.** the first day, **200 mg.** the second day, **100 mg.** the third day; maintenance, **75** to **100 mg.** per day.

USUAL DOSE RANGE—Maintenance, **25** to **250 mg.** per day, as determined by prothrombin time determinations.

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* Patented. See notice, page ii.

Anisindione Tablets

Anisindione Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{12}O_3$.

Identification—

A: Triturate a quantity of finely powdered Anisindione Tablets, equivalent to about 200 mg. of anisindione, with hot benzene, cool, filter, and evaporate to dryness on a steam bath: the residue so obtained responds to the *Identification test* under *Anisindione,* page 55.

B: Dry the remaining residue prepared in *Identification test A* at 105° for 1 hour: the anisindione so obtained melts at about 155°, page 814.

C: The solution prepared for measurement of absorbance in the *Assay* exhibits maxima at about 286 mμ and 338 mμ.

Disintegration, page 878—The disintegration time limit for Anisindione Tablets is 15 minutes.

Content uniformity, *Method I,* page 799—Anisindione Tablets meet the requirements of the content uniformity test for tablets.

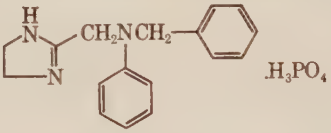
Assay—Weigh and finely powder not less than 20 Anisindione Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of anisindione, to a separator, add 50 ml. of water, and extract with four 45-ml. portions of chloroform, collecting each extract in a 200-ml. volumetric flask. Add chloroform to volume, and mix. Dilute 5.0 ml. of this solution to 50.0 ml. with chloroform, and mix. Transfer 5.0 ml. of this solution to a conical flask, evaporate the chloroform on a steam bath just to dryness, and cool. Dissolve the residue in about 20 ml. of 0.02 *N* alcoholic sodium hydroxide, quantitatively transfer the solution to a 50-ml. volumetric flask, dilute to volume with the alcoholic sodium hydroxide, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Anisindione Reference Standard, in the same medium, at a concentration of about 2.5 mcg. per ml. in 1-cm. cells, at the maximum at about 286 mμ, using 0.02 *N* alcoholic sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_{16}H_{12}O_3$, in the portion of the Tablets taken by the formula $20C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Anisindione Tablets in tight containers.

Tablets available—Anisindione Tablets usually available contain the following amount of anisindione: 50 mg.

CATEGORY and DOSE—See Anisindione.

Antazoline Phosphate



2-[(*N*-Benzylanilino)methyl]-2-imidazoline Phosphate (1:1)

$C_{17}H_{19}N_3 . H_3PO_4$ Mol. wt. 363.36

Antazoline Phosphate contains not less than 98.0 percent and not more than 100.5 percent of $C_{17}H_{19}N_3 . H_3PO_4$, calculated on the dried basis.

Description—Antazoline Phosphate occurs as a white, crystalline powder, possessing a bitter taste.

Solubility—Antazoline Phosphate is soluble in water. It is sparingly soluble in methanol, and is practically insoluble in benzene and in ether.

Identification—

A: To 2 ml. of a solution of Antazoline Phosphate (1 in 100) add 10 drops of nitric acid: the solution turns red and then immediately turns dark green.

B: To 5 ml. of a solution of Antazoline Phosphate (1 to 100) add sufficient sodium hydroxide T.S. to make it distinctly alkaline, collect the precipitate on a filter, wash it with water, and dry: the free base so obtained melts between 118° and 122°, page 814.

C: A solution of Antazoline Phosphate (1 in 100) responds to the tests for *Phosphate*, page 809.

Melting range, page 814—Antazoline Phosphate melts with decomposition between 194° and 198°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Antazoline Phosphate, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Antazoline Phosphate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Antazoline Phosphate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Antazoline Phosphate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 242 mμ, do not differ by more than 2.5 percent.

pH, page 824—The pH of a solution of Antazoline Phosphate (1 in 50) is between 4.0 and 5.0.

Loss on drying, page 814—Dry Antazoline Phosphate at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Assay—Dissolve about 750 mg. of Antazoline Phosphate, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 36.34 mg. of $C_{17}H_{19}N_3.H_3PO_4$.

Packaging and storage—Preserve Antazoline Phosphate in tight containers.

CATEGORY—Antihistaminic.

APPLICATION—1 or 2 drops of a 0.5 percent solution in each eye every 3 or 4 hours.

Antazoline Phosphate Ophthalmic Solution

Antazoline Phosphate Ophthalmic Solution is a sterile solution of antazoline phosphate in water. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{17}H_{19}N_3.H_3PO_4$.

Identification—Antazoline Phosphate Ophthalmic Solution responds to the *Identification tests* under *Antazoline Phosphate,* page 56.

Sterility—Antazoline Phosphate Ophthalmic Solution meets the requirements under *Sterility Tests,* page 874.

Assay—

Standard preparation—Prepare a solution in 0.5 *N* sulfuric acid, containing in each ml. about 500 mcg. of NF Antazoline Phosphate Reference Standard, accurately weighed.

Assay preparation—Transfer a portion of the Antazoline Phosphate Ophthalmic Solution, equivalent to about 25 mg. of antazoline phosphate and accurately measured, to a 50-ml. separator. Add 4 ml. of 0.5 *N* sulfuric acid, and mix thoroughly. Add 20 ml. of ether, shake carefully, and transfer the acid phase to a 125-ml. separator. Shake the ether phase with two successive 2-ml. portions of 0.5 *N* sulfuric acid, transfer each portion of acid into the 125-ml. separator, and discard the ether. To the acid extract, add 5 ml. of sodium hydroxide T.S. and 50 ml. of ether, shake carefully, and transfer the aqueous phase to a second 125-ml. separator containing 50 ml. of ether. Shake this separator carefully, and transfer the aqueous phase to a third 125-ml. separator containing 50 ml. of ether. Shake the third separator carefully, and discard the aqueous phase. Wash the ether extracts in the three separators, in succession, with one 20-ml. portion of water, and discard the water. Extract the separate ether phases successively with 20, 20, and 5 ml. of 0.5 *N* sulfuric acid, combine the acid extracts in a 50-ml. volumetric flask, dilute to volume with the acid, and mix.

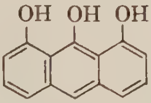
Procedure—Dilute 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* to 250.0 ml. with 0.5 *N* sulfuric acid, and concomitantly determine the absorbances at the maximum at about 242 mμ in 1-cm. cells, with a suitable spectrophotometer, using 0.5 *N* sulfuric acid as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{17}H_{19}N_3.H_3PO_4$ in each ml. of Solution taken by the formula $0.05 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation,* and V is the volume, in ml., of the Solution taken.

Packaging and storage—Preserve Antazoline Phosphate Ophthalmic Solution in well-closed containers.

Solution available—Antazoline Phosphate Ophthalmic Solution usually available contains 0.5 percent of antazoline phosphate.

CATEGORY and APPLICATION—See Antazoline Phosphate.

Anthralin



1,8,9-Anthracenetriol

$C_{14}H_{10}O_3$ Mol. wt. 226.23

Anthralin contains not less than 95.0 percent and not more than 100.5 percent of $C_{14}H_{10}O_3$, calculated on the dried basis.

Description—Anthralin occurs as a yellowish brown, crystalline powder. It is odorless and tasteless.

Solubility—Anthralin is insoluble in water. It is soluble in chloroform, in acetone, in benzene, and in solutions of alkali hydroxides. It is slightly soluble in alcohol, in ether, and in glacial acetic acid.

Identification—

A: Dissolve a few mg. of Anthralin in 5 ml. of sodium hydroxide T.S.: a yellowish to orange solution having a green fluorescence is produced, and when the solution is exposed to air, the color becomes strong orange-red.

B: Dissolve about 100 mg. of Anthralin in 10 ml. of alcohol, and add 0.1 ml. of ferric chloride T.S.: a greenish brown color is produced.

Melting range, page 814—Anthralin melts between 175° and 181°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Anthralin, previously dried over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Anthralin Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Anthralin in chloroform exhibits maxima and minima at the same wavelengths as that of NF Anthralin Reference Standard, similarly measured.

Chloride—Add 1 g. of Anthralin to 15 ml. of water, mix, and filter. To 5 ml. of the filtrate, acidified with nitric acid, add a few drops of silver nitrate T.S.: no more opalescence is produced immediately than is present in a 5-ml. portion of the filtrate to which nothing has been added.

Sulfate—To 5 ml. of the untreated filtrate obtained in the test for *Chloride* add 3 drops of diluted hydrochloric acid and 5 drops of barium chloride T.S.: no more turbidity is produced than is present in a 5-ml. portion of the filtrate to which nothing has been added.

Reaction—Suspend Anthralin in water, and filter: the filtrate is neutral to litmus.

Loss on drying, page 814—Dry Anthralin over silica gel for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 500 mg. of Anthralin is negligible.

Assay—Place about 50 mg. of Anthralin, accurately weighed, in a 50-ml. volumetric flask, add chloroform to volume, and mix. Dilute the solution with chloroform, quantitatively and stepwise, to a concentration of 10 mcg. per ml., and determine the absorbance of this solution in a 1-cm. cell at 354 mμ and at 432 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{14}H_{10}O_3$ in the portion of Anthralin taken by the formula $5000 \times (A_{354}a'_{432} - A_{432}a'_{354})/(a_{354}a'_{432} - a_{432}a'_{354})$, in which A is the absorbance of the solution at the wavelength indicated by the subscript, and a and a' are the absorptivities (see page 866) of NF Anthralin Reference Standard and NF Danthron Reference Standard, respectively, determined in chloroform at the wavelengths indicated by the subscripts.

Packaging and storage—Preserve Anthralin in tight containers, protected from light.

CATEGORY—Local antieczematic.

FOR EXTERNAL USE—Topically, as a 0.1 to 1 percent ointment.

Anthralin Ointment

Anthralin Ointment is anthralin in a petrolatum or other suitable base. Anthralin Ointment labeled to contain more than 0.1 percent of anthralin contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{14}H_{10}O_3$, and that labeled to contain 0.1 percent or less of anthralin contains not less than 90.0 percent and not more than 130.0 percent of the labeled amount of $C_{14}H_{10}O_3$.

Danthron—Using the absorbances determined in the *Assay*, calculate the quantity, in mg., of danthron in the portion of Anthralin Ointment taken for assay by the formula $V \times (A_{432}a_{354} - A_{354}a_{432})/(a_{354}a'_{432} - a_{432}a'_{354})$, in which the symbols are as designated in the *Assay:* the content of danthron ($C_{14}H_8O_4$) is not more than one-tenth of the content of $C_{14}H_{10}O_3$ (anthralin) in Ointment labeled to contain more than 0.1 percent of anthralin, and not more than one-fifth of the content of $C_{14}H_{10}O_3$ (anthralin) in Ointment labeled to contain 0.1 percent or less of anthralin.

Assay—Weigh accurately a quantity of Anthralin Ointment equivalent to about 5 mg. of anthralin, dissolve in chloroform, and dilute quantitatively and stepwise with chloroform to make a solution containing 5 to 10 mcg. of anthralin in each ml. Determine the absorbance of this solution in a 1-cm. cell at 354 mμ and at 432 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{14}H_{10}O_3$ in the portion of Anthralin Ointment taken by the formula $V \times (A_{354}a'_{432} - A_{432}a'_{354})/(a_{354}a'_{432} - a_{432}a'_{354})$, in which V is the total volume, in ml., to which the sample was diluted, A is the absorbance of the solution at the wavelength indicated by the subscript, and *a* and *a′* are the absorptivities (see page 866) of NF Anthralin Reference Standard and NF Danthron Reference Standard, respectively, determined in chloroform at the wavelengths indicated by the subscripts.

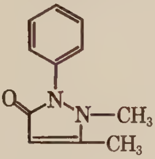
Packaging and storage—Preserve Anthralin Ointment in well-closed, light-resistant containers.

Ointments available—Anthralin Ointment is usually available in the following concentrations: 0.1, 0.25, 0.5 and 1 percent.

CATEGORY and APPLICATION—See Anthralin.

Anticoagulant Sodium Citrate Solution, page 642

Antipyrine



2,3-Dimethyl-1-phenyl-3-pyrazolin-5-one

$C_{11}H_{12}N_2O$ Mol. wt. 188.23

Antipyrine, dried at 60° for 2 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_{11}H_{12}N_2O$.

Description—Antipyrine occurs as colorless crystals, or as a white, crystalline powder. It is odorless, has a slightly bitter taste, and its solutions are neutral to litmus.

Solubility—Antipyrine is very soluble in water, and is freely soluble in alcohol and in chloroform. It is sparingly soluble in ether.

Completeness and color of solution—Antipyrine is completely soluble in its own weight of cold water, the solution being colorless or not more than slightly yellow when viewed transversely in a tube having a diameter of about 20 mm.

Identification—

A: Add tannic acid T.S. to a solution of Antipyrine: a white precipitate is produced.

B: Mix 100 mg. of sodium nitrite and 12 ml. of a solution of Antipyrine (1 in 100): the liquid is nearly colorless, but upon the addition of 1 ml. of diluted sulfuric acid a green color is produced.

C: Add 1 drop of ferric chloride T.S. to 2 ml. of a solution of Antipyrine (1 in 1000): a red color is produced which becomes greenish yellow upon the addition of 10 drops of sulfuric acid.

D: To 100 mg. of Antipyrine add 100 mg. of vanillin, 5 ml. of water, and 2 ml. of sulfuric acid, and heat the mixture to boiling: an orange-yellow precipitate is produced.

Melting range, page 814—Antipyrine melts between 110° and 112.5°.

Loss on drying, page 814—Dry Antipyrine at 60° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Antipyrine yields not more than 0.15 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Antipyrine in 2 ml. of diluted acetic acid, and add sufficient water to make 25 ml.: the heavy metals limit for Antipyrine is 20 parts per million.

Assay—Transfer about 100 mg. of Antipyrine, previously dried at 60° for 2 hours and accurately weighed, to a 250-ml. iodine flask, and dissolve in 25 ml. of water. Add 2 g. of sodium acetate and 20.0 ml. of 0.1 *N* iodine, mix, and allow to stand in a cool, dark place for 20 minutes. Add 25 ml. of alcohol to dissolve the precipitate, and titrate the excess iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 *N* iodine is equivalent to 9.412 mg. of $C_{11}H_{12}N_2O$.

Packaging and storage—Preserve Antipyrine in tight containers.

CATEGORY—Analgesic.

APPLICATION—See Antipyrine and Benzocaine Solution.

Antipyrine and Benzocaine Solution

Antipyrine and Benzocaine Solution is a solution of antipyrine and benzocaine in glycerin. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_{11}H_{12}N_2O$ (antipyrine) and $C_9H_{11}NO_2$ (benzocaine).

Identification—

A: Transfer 5 ml. of Antipyrine and Benzocaine Solution to a separator containing 25 ml. of water, and extract the solution with two 25-ml. portions of a mixture of equal volumes of ether and solvent hexane. Combine the extracts, and retain the water solution for *Identification test B.* Extract the ether-hexane solution with 50 ml. of water and discard the water layer. Evaporate the ether-hexane solution to dryness, dry the residue in vacuum at 40° to 50° for 1 hour, and dissolve the residue in 1 ml. of chloroform: the infrared absorption spectrum of this solution exhibits maxima at the same wavelengths as that of NF Benzocaine Reference Standard, similarly measured.

B: Add 5 ml. of 1 *N* sodium hydroxide solution to the water solution retained from *Identification test A*, and extract with two 25-ml. portions of chloroform. Evaporate the combined extracts to dryness, dry the residue in vacuum at 40° to 50° for 1 hour, and dissolve the residue in 3 ml. of chloroform: the infrared absorption spectrum of this solution exhibits maxima at the same wavelengths as that of NF Antipyrine Reference Standard, similarly measured.

Water, page 900—Determine the water content of Antipyrine and Benzocaine Solution by the titrimetric method: not more than 0.6 percent is found.

Assay for antipyrine—Transfer an accurately measured volume of Antipyrine and Benzocaine Solution, equivalent to about 250 mg. of antipyrine, to a 250-ml. separator. Add 40 ml. of water, extract with four 30-ml. portions of a mixture consisting of equal volumes of ether and solvent hexane, and transfer the aqueous layer to a second separator. To the separator add 10 ml. of sodium carbonate T.S., and extract with four 40-ml. portions of chloroform, collecting the extracts in a 250-ml. volumetric flask. Dilute to volume with chloroform, and mix. Transfer 5.0 ml. of this solution to a second 250-ml. volumetric flask, evaporate to dryness with a stream of nitrogen, add methanol to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Antipyrine Reference Standard in methanol at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 266 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{11}H_{12}N_2O$ in each ml. of the Solution taken by the formula $12.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Solution taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Assay for benzocaine—

Standard preparation—Transfer about 50 mg. of NF Benzocaine Reference Standard, accurately weighed, to a 250-ml. volumetric flask, dissolve in 125 ml. of 0.1 *N* hydrochloric acid, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer an accurately measured volume of Antipyrine and Benzocaine Solution, equivalent to about 50 mg. of benzocaine, to a 250-ml. separator. Add 40 ml. of water, extract with four 30-ml. portions of a mixture consisting of equal volumes of ether and solvent hexane, and transfer the ether-solvent hexane layer to a separator. Wash with 20 ml. of water, discard the washings, and transfer the ether-solvent hexane layer to a 250-ml. round-bottom flask. To the flask add 1 ml. of 1 *N* hydrochloric acid, and evaporate the ether-solvent hexane under reduced pressure. Transfer the residual liquid to a 250-ml. volumetric flask with the aid of several small portions of water, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Transfer 10.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of water to serve as the blank to separate 100-ml. volumetric flasks. To each flask add 40 ml. of water, 10.0 ml. of 1 *N* hydrochloric acid, and 1.0 ml. of sodium nitrite solution (1 in 200), and mix. Allow to stand for 5 minutes, swirling frequently, then add 5.0 ml. of ammonium sulfamate solution (1 in 40), and allow to stand for 10 minutes, swirling frequently. Add 1.0 ml. of *N*-1-naphthyl ethylenediamine dihydrochloride solution (1 in 1000), dilute to volume with water, mix, and allow to stand for 15 minutes, mixing frequently. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 550 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_9H_{11}NO_2$ in each ml. of the Solution taken by the formula 5 × $(C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Solution taken.

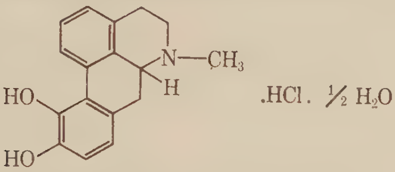
Packaging and storage—Preserve Antipyrine and Benzocaine Solution in tight, light-resistant containers.

Solution available—Antipyrine and Benzocaine Solution usually available contains 5.4 percent of antipyrine and 1.4 percent of benzocaine.

CATEGORY—Local anesthetic.

APPLICATION—Instilled into ear canal from three times a day to every 1 to 2 hours as needed.

Apomorphine Hydrochloride



Aporphine-10,11-diol Hydrochloride

$C_{17}H_{17}NO_2.HCl.{}^1/_2H_2O$ Mol. wt. 312.80

Apomorphine Hydrochloride contains not less than 98.5 percent and not more than 100.5 percent of $C_{17}H_{17}NO_2.HCl$, calculated on the dried basis.

Description—Apomorphine Hydrochloride occurs as minute, white or grayish white, glistening crystals or as a white powder. It is odorless. It gradually acquires a green color on exposure to light and air. Its solutions are neutral to litmus.

Solubility—Apomorphine Hydrochloride is sparingly soluble in water and in alcohol. It is soluble in water at 80°, and is very slightly soluble in chloroform and in ether.

Identification—

A: To 5 ml. of a solution of Apomorphine Hydrochloride (1 in 100) add a slight excess of sodium bicarbonate solution (1 in 20): a white or greenish white precipitate is formed. Add 3 drops of iodine T.S., and shake vigorously: an emerald-green color is produced. Add 5 ml. of ether and, after vigorous shaking, allow the layers to separate: the ether is colored deep ruby-red while the water layer retains its green color.

B: Dissolve Apomorphine Hydrochloride in nitric acid: a dark purple solution is produced.

C: To a solution of Apomorphine Hydrochloride add silver nitrate T.S.: a white precipitate, which is insoluble in nitric acid, is formed. This precipitate soon darkens by reduction to metallic silver, the reduction being accelerated by the addition of ammonia T.S.

Specific rotation, page 822—The specific rotation of Apomorphine Hydrochloride, calculated on the dried basis, determined in a solution in 0.02 N hydrochloric acid containing the equivalent of 150 mg. of Apomorphine Hydrochloride in each 10 ml., is between −49° and −51°.

Loss on drying, page 814—Dry Apomorphine Hydrochloride at 105° for 2 hours: it loses not less than 2 percent and not more than 3.5 percent of its weight.

Residue on ignition, page 858—Apomorphine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Color of solution—Place 100 mg. of Apomorphine Hydrochloride in a suitable test tube, add 10 ml. of cold, oxygen-free water, and agitate gently until dissolved: the color of the resulting solution, observed promptly after the Apomorphine Hydrochloride has dissolved, is not more intense than that of a color standard prepared as directed below. Dissolve 5.0 mg. of Apomorphine Hydrochloride in 100 ml. of water. Pipet 1.0 ml. of this solution into a test tube of the same size as that used for the sample solution, dilute with 6 ml. of water, add 1 ml. of sodium bicarbonate solution (1 in 20), and follow with 0.5 ml. of iodine T.S. Allow to stand for 30 seconds, add 0.6 ml. of 0.1 N sodium thiosulfate, and dilute with water to 10 ml.

Decomposition products—Shake 100 mg. of Apomorphine Hydrochloride with 5 ml. of ether: the latter acquires not more than a pale reddish color.

Assay—Dissolve about 300 mg. of Apomorphine Hydrochloride in 100 ml. of glacial acetic acid with the aid of heat provided by a steam bath. Add 0.1 ml. of acetic anhydride to the hot solution and stir for 5 minutes. Cool to room temperature, add 5 ml. of mercuric acetate T.S., and 0.25 ml. of crystal violet T.S. and titrate with 0.1 N perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 30.38 mg. of $C_{17}H_{17}NO_2.HCl$.

Packaging and storage—Preserve Apomorphine Hydrochloride in small, tight, light-resistant containers. Containers from which Apomorphine Hydrochloride is to be taken for immediate use in compounding prescriptions contain not more than 350 mg.

CATEGORY—Emetic.

USUAL DOSE—Subcutaneous, **5 mg.**

Apomorphine Hydrochloride Tablets

Apomorphine Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{17}NO_2.HCl.{}^1/_2H_2O$.

Identification—To 5 ml. of a filtered solution of Apomorphine Hydrochloride Tablets, containing about 10 mg. of apomorphine hydrochloride, add sodium bicarbonate solution: a white or greenish precipitate is formed which rapidly becomes green on exposure to air. When the mixture is shaken with a few ml. of ether, the ether acquires a violet color, and the water solution an emerald-green color.

Color of solution—Dissolve a quantity of powdered Apomorphine Hydrochloride Tablets, equivalent to 5 mg. of apomorphine hydrochloride, in sufficient water to make 100.0 ml. Transfer 1.0 ml. of the solution to a test tube, dilute with 6 ml. of water and, if necessary, filter through a small pledget of cotton. Add 1 ml. of sodium bicarbonate solution (1 in 20) and follow with 0.5 ml. of iodine T.S. Allow to stand for 30 seconds, then add 0.6 ml. of 0.1 *N* sodium thiosulfate, and dilute with water to 10.0 ml. This solution represents the color standard.

Place a quantity of powdered Apomorphine Hydrochloride Tablets, equivalent to 50 mg. of apomorphine hydrochloride, in a test tube of suitably small size, add 10.0 ml. of cold, oxygen-free water, stopper the test tube, and agitate gently until no more dissolves; if necessary, filter at once through a small pledget of cotton. The color of the solution, observed promptly after preparation, is not more intense than that of the color standard. Use closely matched test tubes for the comparison.

Disintegration, page 878—The disintegration time limit for Apomorphine Hydrochloride Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Apomorphine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets using the following special procedure: Place one tablet in a 500-ml. volumetric flask containing 100 ml. of 0.1 *N* hydrochloric acid, and shake for 15 minutes. Dilute to volume with 0.1 *N* hydrochloric acid, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with 0.1 *N* hydrochloric acid to provide a solution containing approximately 12 mcg. of apomorphine hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a standard solution of NF Apomorphine Hydrochloride, in the same medium, at a concentration of about 12 mcg. per ml., in 1-cm. cells, at the maximum at about 273 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{17}H_{17}NO_2.HCl.{}^1/_2H_2O$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of apomorphine hydrochloride in the tablet; D is the exact concentration, in mcg. per ml., of apomorphine hydrochloride in the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of $C_{17}H_{17}NO_2.HCl.{}^1/_2H_2O$ in the standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the standard solution.

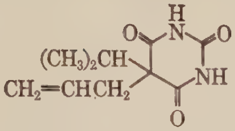
Assay—Weigh and finely powder not less than 20 Apomorphine Hydrochloride Tablets. Dissolve an accurately weighed portion of the powder, equivalent to about 50 mg. of apomorphine hydrochloride, in 25 ml. of water in a separator, add 500 mg. of sodium bicarbonate, and completely extract with successive small portions of ether. Combine the ether extracts and wash them with three 5-ml. portions of water. Shake the combined water washings with 10 ml. of ether and add this ether to the combined ether extracts. To the ether solution add 20.0 ml. of 0.02 *N* sulfuric acid, stir thoroughly, and warm until the ether is expelled. Cool, if necessary, add 3 drops of methyl red T.S., and titrate the excess acid with 0.02 *N* sodium hydroxide. Each ml. of 0.02 *N* sulfuric acid is equivalent to 6.256 mg. of $C_{17}H_{17}NO_2.HCl.{}^1/_2H_2O$.

Packaging and storage—Preserve Apomorphine Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Apomorphine Hydrochloride Tablets usually available contain the following amount of apomorphine hydrochloride: 6 mg.

CATEGORY and DOSE—See Apomorphine Hydrochloride.

Aprobarbital



5-Allyl-5-isopropylbarbituric Acid

$C_{10}H_{14}N_2O_3$ Mol. wt. 210.23

Aprobarbital, dried at 105° for 2 hours, contains not less than 98.5 percent and not more than 101.0 percent of $C_{10}H_{14}N_2O_3$.

Description—Aprobarbital occurs as a fine, white, odorless, crystalline powder, having a slightly bitter taste. It is stable in air. A saturated solution is acid to litmus.

Solubility—Aprobarbital is slightly soluble in cold water. It is soluble in alcohol, in chloroform, and in ether.

Identification—

A: Boil about 300 mg. of Aprobarbital with 10 ml. of sodium hydroxide solution (1 in 10): ammonia is evolved.

B: Shake about 300 mg. of Aprobarbital for 2 minutes with 1 ml. of sodium hydroxide T.S. and 5 ml. of water, filter, and divide the filtrate into 2 portions. To one portion add mercuric nitrate T.S.: a white precipitate is formed which is soluble in ammonia T.S. To the other portion add silver nitrate T.S., a few drops at a time: a white precipitate forms which at first redissolves, but becomes insoluble when an excess of silver nitrate has been added.

C: Dissolve about 100 mg. of Aprobarbital in 10 ml. of hot water, cool, filter, and divide the filtrate into two portions. To one portion add 1 ml. of acetic acid and 1 ml. of bromine T.S.: the bromine color is discharged immediately. To the other portion add 1 ml. of potassium permanganate T.S.: a yellow color is produced immediately which turns brown.

Melting range, page 814—Aprobarbital melts between 140° and 143°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Aprobarbital, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Aprobarbital Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 75,000 solution of Aprobarbital in 0.1 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Aprobarbital Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 242 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Aprobarbital at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Aprobarbital yields not more than 0.1 percent of residue on ignition.

Readily carbonizable substances, page 856—Dissolve 500 mg. of Aprobarbital in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid A.

Assay—Dissolve about 200 mg. of Aprobarbital, previously dried at 105° for 2 hours and accurately weighed, in 20 ml. of dimethylformamide in a 100-ml. conical flask. Add 4 drops of thymol blue solution (1 in 200 in methanol) and titrate with 0.1 *N* lithium methoxide using a 10-ml. buret, a magnetic stirrer, and a cover for the flask to protect against atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* lithium methoxide is equivalent to 21.02 mg. of $C_{10}H_{14}N_2O_3$.

Packaging and storage—Preserve Aprobarbital in well-closed containers.

CATEGORY—Sedative.

USUAL DOSE RANGE—Sedative, **20** to **40 mg.** three times daily; hypnotic, **40** to **160 mg.** at night.

Aprobarbital Elixir

Aprobarbital Elixir contains not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $C_{10}H_{14}N_2O_3$.

Identification—Transfer 30 ml. of Aprobarbital Elixir to a separator, extract with 50 ml. of ether, and evaporate the solvent on a steam bath in a conical flask, with the aid of a stream of nitrogen.

A: Shake one half of the residue

with 1 ml. of sodium hydroxide T.S. and 5 ml. of water, and filter. To the clear filtrate add mercuric nitrate T.S.: a white precipitate is formed which is soluble in ammonia T.S.

B: Dissolve the remaining residue in 10 ml. of hot water, cool, and filter. To the clear filtrate add 1 ml. of acetic acid and 1 ml. of bromine T.S.: the bromine color is discharged immediately.

Assay—Transfer an accurately measured volume of Aprobarbital Elixir, equivalent to about 200 mg. of aprobarbital, to a 250-ml. separator, add 50 ml. of water and 10 ml. of diluted hydrochloric acid, and extract with four 30-ml. portions of ether. Combine the ether extracts, and wash them with two 10-ml. portions of water. Shake the combined water washings with 10 ml. of ether, and add the ether to the combined ether extracts. Evaporate the ether on a steam bath, with the aid of a stream of nitrogen, dissolve the residue in 25 ml. of dehydrated alcohol, and evaporate the alcohol on a steam bath, with the aid of a stream of nitrogen. Dissolve the residue in 25 ml. of water by heating on a steam bath, cool, add 50 ml. of hydrochloric acid, and titrate with 0.1 *N* bromine, determining the end-point potentiometrically using suitable electrodes. Each ml. of 0.1 *N* bromine is equivalent to 10.51 mg. of $C_{10}H_{14}N_2O_3$.

Alcohol content—Determine the alcohol content by the gas-liquid chromatographic procedure, page 773, using *n*-propyl alcohol as the internal standard. Aprobarbital Elixir contains from 20 to 21.5 percent (v/v) of C_2H_5OH.

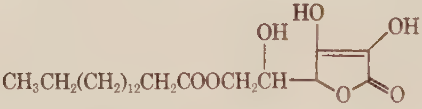
Packaging and storage—Preserve Aprobarbital Elixir in tight, light-resistant containers.

Elixir available—Aprobarbital Elixir usually available contains the following amount of aprobarbital: 40 mg. in 5 ml.

CATEGORY and DOSE—See Aprobarbital.

Aromatic Ammonia Spirit, page 42
Aromatic Castor Oil, page 142
Aromatic Eriodictyon Syrup, page 272

Ascorbyl Palmitate



L-Ascorbic Acid 6-Palmitate

$C_{22}H_{38}O_7$ Mol. wt. 414.54

Ascorbyl Palmitate contains not less than 95.0 percent and not more than 100.5 percent of $C_{22}H_{38}O_7$, calculated on the dried basis.

Description—Ascorbyl Palmitate occurs as a white to yellowish white powder having a characteristic odor.

Solubility—Ascorbyl Palmitate is very slightly soluble in water and in vegetable oils. It is soluble in alcohol.

Identification—Dissolve 1 g. of Ascorbyl Palmitate in 25 ml. of alcohol and add a 1 in 1000 solution of 2,6-dichlorophenolindophenol sodium: the resultant mixture is colorless.

Melting range, *Class Ia*, page 814—Ascorbyl Palmitate melts between 107° and 117°.

Specific rotation, page 822—The specific rotation of Ascorbyl Palmitate, determined in a solution in methanol containing 1 g. of Ascorbyl Palmitate in each 10 ml., calculated on the dried basis, is between +21° and +24°.

Loss on drying, page 814—Dry Ascorbyl Palmitate in vacuum at 60° for 1 hour: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Ascorbyl Palmitate yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Ascorbyl Palmitate is 10 parts per million.

Assay—Dissolve about 300 mg. of Ascorbyl Palmitate, accurately weighed, in 50 ml. of alcohol, add 30 ml. of water, and immediately titrate with 0.1 *N* iodine to a yellow color which persists for at least 30 seconds. Each ml. of 0.1 *N* iodine is equivalent to 20.73 mg. of $C_{22}H_{38}O_7$.

Packaging and storage—Preserve Ascorbyl Palmitate in tight containers, preferably in a cool, dry place.

CATEGORY—Preservative (antioxidant).

Aspirin, Aluminum, page 30
Aspirin, Aluminum, Tablets, page 31

Aspirin Capsules

Aspirin Capsules contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_9H_8O_4$.

Identification—

A: Heat about 100 mg. of the contents of Aspirin Capsules with 10 ml. of water for several minutes, cool, and add 1 drop of ferric chloride T.S.: a violet-red color is produced

B: Boil about 500 mg. of the contents of Aspirin Capsules with 10 ml. of sodium hydroxide T.S. for a few minutes, cool, and add 10 ml. of diluted sulfuric acid: a white precipitate of salicylic acid is formed and the odor of acetic acid is perceptible. Filter, add to the filtrate 3 ml. of alcohol and 3 ml. of sulfuric acid, and warm: the odor of ethyl acetate is perceptible.

Weight variation, page 901—Aspirin Capsules meet the requirements of the weight variation test for capsules.

Free salicylic acid—

Ferric chloride-urea reagent—Dissolve by swirling, without the aid of heat, 60 g. of urea in a mixture of 8 ml. of ferric chloride solution (6 in 10) and 42 ml. of 0.05 *N* hydrochloric acid. Adjust the resulting solution to a pH of 3.2, if necessary, by the addition of 6 *N* hydrochloric acid.

Standard preparation—Transfer 75.0 mg. of salicylic acid, previously dried over silica gel for 3 hours and accurately weighed, to a 100-ml. volumetric flask, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this last solution to a 50-ml. volumetric flask containing 10 ml. of methanol, 2 drops of hydrochloric acid, and 10 ml. of a 1 in 10 solution of glacial acetic acid in ether, dilute to volume with chloroform, and mix.

Test preparation—Pack a pledget of glass wool in the base of a 25 × 200-mm. chromatographic tube, and uniformly pack the tube with a mixture of 3 g. of chromatographic siliceous earth and 2 ml. of freshly prepared *Ferric chloride-urea reagent.* Weigh accurately an amount of the contents of Aspirin Capsules, equivalent to 100.0 mg. of aspirin, mix with 10 ml. of chloroform by stirring for 3 minutes, and then transfer to the chromatographic column with the aid of a few ml. of chloroform. Pass 50 ml. of chloroform through the column, rinse the tip of the chromatographic tube with chloroform, and discard the eluate. Prepare as a receiver a 50-ml. volumetric flask containing 10 ml. of methanol and 2 drops of hydrochloric acid, and elute any salicylic acid from the column by passing 10 ml. of a 1 in 10 solution of glacial acetic acid in ether that has been recently saturated with water, followed by 30 ml. of chloroform. Dilute the eluate to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbance of the solutions in 1-cm. cells, at the maximum at about 306 mμ, with a suitable spectrophotometer, using as the blank a solvent mixture of the same composition as that used for the *Standard preparation:* the absorbance of the *Test preparation* does not exceed that of the *Standard preparation* (0.75 percent, calculated on the labeled aspirin content).

Assay—[Note—In this assay use chloroform recently saturated with water.]

Chromatographic column—Insert a small pledget of glass wool above the stem constriction of a 25 × 200-mm. chromatographic tube, and uniformly pack with a mixture of about 3 g. of granular, 80 to 100-mesh, chromatographic siliceous earth and 2 ml. of freshly prepared sodium bicarbonate solution (1 in 12).

Standard preparation—Transfer about 50 mg., accurately weighed, of USP Aspirin Reference Standard to a 50-ml. volumetric flask, add 0.5 ml. of glacial acetic acid, and add chloroform to volume. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, add a 1 in 100 solution of glacial acetic acid in chloroform to volume, and mix.

Assay preparation—Remove as completely as possible, the contents of not less than 20 Aspirin Capsules, and weigh accurately. Mix the combined contents thoroughly, and transfer an accurately weighed quantity of the powder, equivalent to about 50 mg. of aspirin, to a 50-ml. volumetric flask containing 1 ml. of a 1 in 50 solution of hydrochloric acid in methanol, add chloroform to volume, and mix.

Procedure—Pipet 5.0 ml. of the *Assay preparation* into the column, wash with 5 ml. and then with 25 ml. of chloroform, and discard the washings. Elute into a 100-ml. volumetric flask with about 10 ml. of a 1 in 10 solution of glacial acetic acid in chloroform, and then with about 85 ml. of a 1 in 100 solution of glacial acetic acid in chloroform, dilute with the latter solvent to volume, and mix. Without delay, concomitantly determine the absorbances of the eluted *Assay preparation* and the *Standard preparation,* in 1-cm. cells, at the wavelength of maximum absorbance at about 280 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_9H_8O_4$ in the portion of the Capsules taken by the formula $C \times (A_U/A_S)$, in which C is the concentration, in mcg. per ml., of the *Standard preparation*, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.

Packaging and storage—Preserve Aspirin Capsules in well-closed containers.

Capsules available—Aspirin Capsules usually available contain the following amount of aspirin: 300 mg.

CATEGORY—Analgesic.

USUAL DOSE OF ASPIRIN—**300** to **600 mg.** every 4 hours.

Aspirin, Phenacetin and Caffeine Tablets

Aspirin, Phenacetin and Caffeine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_9H_8O_4$ (aspirin), $C_{10}H_{13}NO_2$ (phenacetin), and $C_8H_{10}N_4O_2$ (caffeine).

Identification—

A: Crush an Aspirin, Phenacetin and Caffeine Tablet, boil it with 5 ml. of sodium hydroxide T.S. for a few minutes, cool, filter, and add 10 ml. of diluted sulfuric acid to the filtrate: a white precipitate of salicylic acid is formed. Filter and divide the filtrate into two parts. To one part of the filtrate add 1 ml. of alcohol and 1 ml. of sulfuric acid, and warm: the odor of ethyl acetate is perceptible. To the other portion of the filtrate add 1 or 2 drops of ferric chloride T.S., mix, and neutralize with ammonia T.S.: a violet to purple color is produced (*presence of aspirin*).

B: Boil about 200 mg. of the residue obtained in *Identification test A* for 1 minute with 1 ml. of hydrochloric acid, dilute with 10 ml. of water, cool, filter, and add 1 drop of potassium dichromate T.S. to the filtrate: the mixture slowly develops a ruby-red color (*presence of phenacetin*).

C: Crush one Aspirin, Phenacetin and Caffeine Tablet into a small evaporating dish, add 1 ml. of hydrochloric acid and 100 mg. of potassium chlorate, and evaporate to dryness on a steam bath. Invert the dish over a vessel containing a few drops of ammonia T.S.: the residue acquires a purple color, which disappears upon the addition of a solution of a fixed alkali (*presence of caffeine*).

Disintegration, page 878—The disintegration time limit for Aspirin, Phenacetin and Caffeine Tablets is 10 minutes.

Content uniformity, *Method I*, page 799—Aspirin, Phenacetin and Caffeine Tablets meet the requirements of the content uniformity test for tablets with respect to caffeine content.

Free salicylic acid—

Ferric chloride-urea reagent—Dissolve by swirling, without the aid of heat, 60 g. of urea in a mixture of 8 ml. of ferric chloride solution (6 in 10) and 42 ml. of 0.05 *N* hydrochloric acid. Adjust the resulting solution to a pH of 3.2, if necessary, by the addition of 6 *N* hydrochloric acid.

Standard preparation—Transfer 75.0 mg. of salicylic acid, previously dried over silica gel for 3 hours and accurately weighed, to a 100-ml. volumetric flask, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this last solution to a 50-ml. volumetric flask containing 10 ml. of methanol, 2 drops of hydrochloric acid, and 10 ml. of a 1 in 10 solution of glacial acetic acid in ether, dilute to volume with chloroform, and mix.

Test preparation—Pack a pledget of glass wool in the base of a 25 × 200-mm. chromatographic tube, and uniformly pack the tube with a mixture of 3 g. of chromatographic siliceous earth and 2 ml. of freshly prepared *Ferric chloride-urea reagent*. Weigh accurately a quantity of finely powdered Aspirin, Phenacetin and Caffeine Tablets, equivalent to 100.0 mg. of aspirin, mix with 10 ml. of chloroform by stirring for 3 minutes, and then transfer to the chromatographic column with the aid of a few ml. of chloroform. Pass 50 ml. of chloroform through the column, rinse the tip of the chromatographic tube with chloroform, and discard the eluate. Prepare as a receiver a 50-ml. volumetric flask containing 10 ml. of methanol and 2 drops of hydrochloric acid, and elute any salicylic acid from the column by passing 10 ml. of a 1 in 10 solution of glacial acetic acid in ether that has been recently saturated with water, followed by 30 ml. of chloroform. Dilute the eluate to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 306 mμ, with a suitable spectrophotometer, using as the blank a solvent mixture of the same composition as that used for the *Standard preparation:* the absorbance of the *Test* *preparation* does not exceed that of the *Standard preparation* (0.75 percent, calculated on the labeled aspirin content).

Assay—

Preparation of chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 200-mm. test tube to which is fused a 5-cm. length of 6 or 8-mm. tubing) with the aid of a tamping rod of stainless steel, aluminum, or glass, at least 30 cm. long and having a disk with a diameter about 1 mm. less than that of the chromatographic tube. To 2.0 g. of purified siliceous earth (see page 927) in a glass mortar add 2.0 ml. of approximately 4 *N* sulfuric acid and incorporate by kneading thoroughly with a flexible spatula blade until the mixture is fluffy. Transfer to the column and tamp gently to compress the material to a uniform mass. In like manner, mix intimately 2.0 g. of purified siliceous earth with 2.0 ml. of approximately 1 *N* sodium bicarbonate, transfer to the column, and gently compress with the tamping rod. Wash the column so prepared with one 20-ml. portion of water-washed ether and discard the washings.

Phenacetin standard solution—Transfer to a 100-ml. volumetric flask about 50 mg. of USP Phenacetin Reference Standard, previously dried at 60° for 1 hour and accurately weighed, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, add isooctane to volume, and mix.

Aspirin standard solution—Transfer to a 100-ml. volumetric flask about 50 mg. of USP Aspirin Reference Standard, dried over silica gel for 5 hours, and accurately weighed. Add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, add 1 ml. of glacial acetic acid, dilute to volume with chloroform, and mix. Use within 3.5 hours.

Caffeine standard solution—Transfer to a 100-ml. volumetric flask about 100 mg. of NF Caffeine Reference Standard, previously dried at 80° for 4 hours and accurately weighed, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparation—Weigh and finely powder not less than 20 Aspirin, Phenacetin and Caffeine Tablets. Transfer to a 50-ml. volumetric flask an accurately weighed portion of the powder, equivalent to about 50 mg. of aspirin, add 30 ml. of chloroform, and mix thoroughly by shaking. Add 0.1 ml. of glacial acetic acid, dilute to volume with chloroform, and mix.

Procedure—(Use water-washed solvents.) Dilute 5.0 ml. of the *Assay preparation* with 20 ml. of ether and pass the solution into the column without pressure. After all of the solution has passed into the column, complete the elution of the phenacetin from the column with five 5-ml. portions of ether, allowing each portion to pass into the column before the next portion is added, and collecting the total ether eluate in a glass evaporating dish. Immediately after the last portion of ether has passed through the column, rinse the tip of the outlet tube with chloroform, collecting the rinsings in the evaporating dish, remove the dish, and replace it with a 50-ml. volumetric flask to receive the caffeine eluate in the next step. Evaporate the total eluate to dryness on a steam bath in a current of air. Dissolve the residue in 5 ml. of chloroform, transfer to a 50-ml. volumetric flask, dilute to volume with isooctane, and mix.

To elute the caffeine, pass 48 ml. of chloroform through the column, rinse the tip with chloroform, and add sufficient chloroform to make 50.0 ml. Replace the receiver with a 100-ml. volumetric flask, and elute the aspirin with a solution of 0.5 ml. of glacial acetic acid in 5 ml. of chloroform, followed by 90 ml. of a solution of glacial acetic acid in chloroform (1 in 100), dilute to volume with the latter solvent, and mix. The absorbance of the aspirin solution must be determined within 3.5 hours after preparation of the *Assay preparation*.

Determine the absorbance of each solution in 1-cm. cells, with a suitable spectrophotometer, at 285 mμ for the phenacetin solutions, at 276 mμ for the caffeine solutions, and at 280 and 310 mμ for the aspirin solutions, using as a blank the respective solvent employed for each solution. Record the absorbance of each *Standard solution* as A_S and that of the corresponding *Assay solution* as A_U.

Calculation for phenacetin—Calculate the quantity, in mg., of $C_{10}H_{13}NO_2$ per tablet by the formula $0.5C \times (A_U/A_S) \times$ (Av. Wt. per Tablet/Wt. of Sample), in which C is the exact quantity, in mcg., of phenacetin per ml. of the *Phenacetin standard solution*.

Calculation for aspirin—Calculate the quantity, in mg., of $C_9H_8O_4$ per tablet by the formula $C \times [(A_{U280} - 0.2A_{U310})/A_{S280}] \times$ (Av. Wt. per Tablet/Wt. of Sample), in which C is the exact quantity, in mcg., of aspirin per ml. of the *Aspirin standard solution*, and A_U and A_S are the absorbances of the sample solution and standard solution, respectively, at the wavelengths indicated by the subscripts.

Calculation for caffeine—Calculate the quantity, in mg., of $C_8H_{10}N_4O_2$ per tablet by the formula $0.5C \times (A_U/A_S) \times$ (Av. Wt. per Tablet/Wt. of Sample), in which C is the exact quantity, in mcg., of caffeine per ml. of the *Caffeine standard solution*.

Packaging and storage—Preserve Aspirin, Phenacetin, and Caffeine Tablets in well-closed containers.

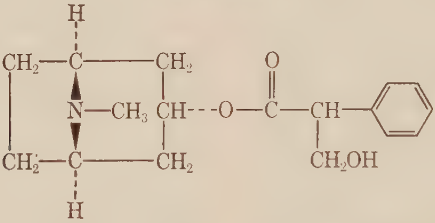
Tablets available—Aspirin, Phenacetin and Caffeine Tablets usually available contain the following amount of aspirin: 230 mg.; of phenacetin: 150 mg.; and of caffeine: 15 and 30 mg.

CATEGORY—Analgesic.

USUAL DOSE OF ASPIRIN—**300** to **600 mg.**; OF PHENACETIN—**300 mg.**; OF CAFFEINE—**200 mg.**

Aspirin, Phenacetin, Caffeine, and Codeine Phosphate Tablets, page 178
Aspirin and Propoxyphene Hydrochloride Capsules, page 606

Atropine



1αH,5αH-Tropan-3α-ol (±)-Tropate (Ester)

$C_{17}H_{23}NO_3$ Mol. wt. 289.38

Atropine contains not less than 99.0 percent and not more than 100.5 percent of $C_{17}H_{23}NO_3$.

Caution: Atropine is extremely poisonous.

Description—Atropine occurs as white crystals, usually needle-like, or as a white, crystalline powder. Its saturated solution is alkaline to phenolphthalein T.S. It is optically inactive, but usually contains some levorotatory hyoscyamine.

Solubility—Atropine is slightly soluble in water and sparingly soluble in water at 80°. It is freely soluble in alcohol and in chloroform, and is soluble in glycerin and in ether.

Identification—

A: To about 10 mg. of Atropine contained in a porcelain dish, add a few drops of fuming nitric acid, and evaporate to dryness on a steam bath: a yellow residue is obtained. To the cooled residue add a few drops of alcoholic potassium hydroxide T.S. and a fragment of potassium hydroxide: the mixture is intensely violet in color (*hyoscyamine* and *scopolamine*, similarly treated, produce the same color as Atropine, but the presence of *other alkaloids* obscures the color effect).

B: To a solution of Atropine (1 in 50) in diluted hydrochloric acid, add gold chloride T.S.: a lusterless precipitate is produced (*hyoscyamine* similarly treated yields a lustrous precipitate).

Melting range, page 814—Atropine melts between 114° and 118°.

Residue on ignition, page 858—Atropine yields not more than 0.1 percent of residue on ignition.

Readily carbonizable substances, page 856—Dissolve 200 mg. of Atropine in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid A and the solution is colored no more than light yellow upon the addition of 0.2 ml. of nitric acid.

Other alkaloids—Dissolve 200 mg. of Atropine in 1 ml. of 1 *N* hydrochloric acid and sufficient water to make 15.0 ml. of solution. To 5 ml. of the solution add a few drops of platinic chloride T.S.: no precipitate is formed. To a separate 5-ml. portion of the solution add 2 ml. of ammonia T.S., and shake vigorously: a slight opalescence may develop but no turbidity is produced.

Hyoscyamine—Dissolve 1 g. of Atropine, previously dried at 105° for 1 hour, in sufficient 50 percent alcohol (w/w) to make a volume of 20 ml. at 25°: the angular rotation of this solution, using a 200-mm. tube, does not exceed −0.70°, page 822.

Assay—Dissolve about 400 mg. of Atropine, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 28.94 mg. of $C_{17}H_{23}NO_3$.

Packaging and storage—Preserve Atropine in tight, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**250 mcg.** three times a day.

Atropine and Morphine Sulfates Tablets, page 464
Atropine Sulfate and Diphenoxylate Hydrochloride Solution, page 256
Atropine Sulfate and Diphenoxylate Hydrochloride Tablets, page 257

Azuresin*

Azure A Carbacrylic Resin

Azuresin is a complex combination of 3-amino-7-(dimethylamino)-phenazathionium chloride, known as azure A dye, and a carbacrylic cationic exchange resin. It contains, in each g., not less than 50 mg. and not more than 70 mg. of the dye, calculated on the dried basis.

Description—Azuresin occurs as moist, irregular, dark blue or purple colored granules. It has a slightly pungent odor.

Identification—To 2 g. of Azuresin add 50 ml. of water: the water does not acquire more than a slightly blue color. Add 2 ml. of 1 *N* hydrochloric acid: the water acquires a deep blue color.

Loss on drying, page 814—Dry Azuresin in vacuum at 38° for 18 hours: it loses not less than 18 percent and not more than 35 percent of its weight.

Elution test—Transfer 1.0 ± 0.005 g. of Azuresin, accurately weighed, into each of two glass-stoppered conical flasks. To one flask add 100 ml. of water that previously has been adjusted with hydrochloric acid to pH 1.5, and to the other add 100 ml. of water that has been adjusted with hydrochloric acid to pH 3.0. Close the flasks, and shake mechanically for 1 hour. Then determine the pH of the contents of each flask: in neither case has the pH changed by more than 0.10 unit.

Allow the resin in each flask to settle, and pipet 5.0 ml. of each of the supernatant solutions into separate, 500-ml. volumetric flasks, add 0.1 *N* hydrochloric acid to volume, and mix. Determine the absorbance of each solution in a 1-cm. cell at the maximum at about 630 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank: the absorbance of the solution prepared from the Azuresin held at pH 3.0 is not more than 0.1 *A* and that of the solution from Azuresin held at pH 1.5 is not less than 0.3 *A*, in which *A* is the absorbance at 690 mμ of the acid–alcohol solution prepared and measured in the *Assay.*

Assay—Transfer 500 ± 5 mg. of Azuresin, accurately weighed, to a glass-stoppered, 1000-ml. volumetric flask. Add, with shaking, sufficient of a mixture of 1 volume of hydrochloric acid and 2 volumes of diluted alcohol to make 1000.0 ml. Shake for 4 hours, and allow to stand overnight. Pipet 10.0 ml. of the supernatant liquid into a 50-ml. volumetric flask, dilute with the acid-alcohol mixture to volume, and mix. Concomitantly determine the absorbance of this solution and a solution of NF Azure A Reference Standard, in the same medium, at a concentration of about 6 mcg. per ml. in 1-cm. cells, at the maximum at about 690 mμ, with a suitable spectrophotometer, using the acid alcohol as the blank. Calculate the quantity, in mg., of Azure A dye in each g. of the resin by the formula $5 \times (C/W) \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, A_S is the absorbance of the Reference Standard solution, and W is the amount, in g., of Azuresin taken, corrected to the dried basis.

Packaging and storage—Preserve Azuresin in tight containers in the form of sealed packets.

Category—Diagnostic aid (gastric secretion).

Usual Dose—**2 g.** preceded by **500 mg.** of Caffeine and Sodium Benzoate.

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* Patented. See notice, page ii.

Bacitracin, Zinc, Neomycin Sulfate, and Polymyxin B Sulfate Ointment, page 475
Basic Fuchsin, page 322

Belladonna Extract

Belladonna Extract contains, in each 100 g., not less than 1.15 g. and not more than 1.35 g. of the alkaloids of belladonna leaf.

PILULAR BELLADONNA EXTRACT

Prepare an extract by percolating 1000 g. of belladonna leaf, using a mixture of 3 volumes of alcohol and 1 volume of water as the menstruum. Macerate the drug during 16 hours and then percolate it at a moderate rate. Evaporate the percolate to a pilular consistence under reduced pressure and at a temperature not exceeding 60°, and adjust the remaining extract, after assaying, by dilution with liquid glucose so that the finished Extract will contain, in each 100 g., 1.25 g. of the alkaloids of belladonna leaf.

Assay—Weigh accurately 3 g. of Pilular Belladonna Extract and mix with a suitable quantity of adsorbent (see *Alkaloidal Drug Assays*, page 774). Transfer completely, with the aid of a few ml. of alcohol or ether, to an extraction thimble, insert the thimble in a continuous-extraction apparatus, moisten with a mixture of 3 ml. of stronger ammonia water, 5 ml. of alcohol, and 10 ml. of ether, and mix thoroughly. Macerate overnight, and extract it for not less than 3 hours or until completely extracted (see *Extraction of Drugs*, page 774), using ether as the solvent. Transfer the liquid to a separator, rinse the container with 1 or more small volumes of the solvent, and add the rinsings to the separator. Completely remove the alkaloids from the immiscible solvent by extracting with successive portions of approximately 0.5 *N* sulfuric acid (see *Purification of the Alkaloids* under *Proximate Assays*, page 774), filtering each portion drawn off. Render the combined acid solutions distinctly alkaline with ammonia T.S., and completely remove the alkaloids at once by extracting with successive portions of chloroform. Evaporate the combined chloroform extracts to dryness on a steam bath and keep the dry residue at this temperature for 15 minutes. Again dissolve the residue in chloroform, evaporate to dryness on a steam bath, and continue the heating for 15 minutes. Dissolve, evaporate, and heat for the third time. Dissolve the resulting residue in a few ml. of chloroform, add 15.0 ml. of 0.02 *N* sulfuric acid, remove the chloroform by evaporation, cool, add 3 drops of methyl red T.S., and titrate the excess acid with 0.02 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.02 *N* sulfuric acid is equivalent to 5.788 mg. of belladonna alkaloids.

The following alternate process for the extraction of the alkaloids may be used: Weigh accurately about 3 g. of Pilular Belladonna Extract, and intimately mix it with two to three times its weight of washed sand. Place the mixture in a sintered-glass funnel of about 50 ml. capacity, and insert the stem of the funnel in a 50-ml. test tube placed in a suction flask. To the funnel add 20 ml. of a mixture of 8 ml. of stronger ammonia water, 20 ml. of ether, and 10 ml. of chloroform, and allow to macerate for 30 minutes, keeping the funnel covered to prevent evaporation. Now apply slight suction until the contents of the funnel are dry. Release the suction, and transfer the filtrate to a separator. Repeat, in the same manner, the extraction of the contents of the funnel four times, using 10 ml. of ether each time, and reducing the maceration time to 5 minutes. Wash the residue in the funnel with three or more 10-ml. portions of approximately 0.5 *N* sulfuric acid until 1 ml. of the last washing gives a negative test with mercuric-potassium iodide T.S. (see *Purification of the Alkaloids* under *Proximate Assays*, page 774). Using these acid washings for removing the alkaloids from the immiscible solvent, proceed as directed above, beginning with "Completely remove the alkaloids from the immiscible solvent. . . ."

POWDERED BELLADONNA EXTRACT

Prepare an extract by percolating 1000 g. of belladonna leaf, using alcohol as the menstruum. Macerate the drug during 16 hours and then percolate it slowly. Evaporate the percolate to a soft extract under reduced pressure and at a temperature not exceeding 60°, add 50 g. of dry starch, and continue the evaporation, at the same temperature, until the product is dry. Powder the residue. The extract may be deprived of its fat by treating either the soft extract first obtained, or the dry and powdered extract, as directed under *Extracts*, page 828. Assay the powdered residue and add sufficient starch, dried at 100°, to make the finished Extract contain, in each 100 g., 1.25 g. of the alkaloids of belladonna leaf. Mix the powders thoroughly and pass the Extract through a fine sieve.

Assay—Weigh accurately about 3 g. of Powdered Belladonna Extract, place it in an extraction thimble, insert the thimble in a continuous-extraction apparatus, moisten the Extract with a mixture of 3 ml. of stronger ammonia water, 5 ml. of alcohol, and 10 ml. of ether, and mix thoroughly. Macerate overnight, and extract it for not less than 3 hours or until completely extracted (see *Extraction of Drugs*, page 774), using ether as the solvent. Then proceed as directed in the *Assay* under *Pilular Belladonna Extract*, page 70, beginning with "Transfer the liquid to a separator. . . ."

Powdered Belladonna Extract may also be assayed by the alternate method described under *Pilular Belladonna Extract*. Each ml. of 0.02 *N* sulfuric acid is equivalent to 5.788 mg. of belladonna alkaloids.

Packaging and storage—Preserve Belladonna Extract in tight containers, preferably at a temperature not above 30°.

CATEGORY—Anticholinergic.
USUAL DOSE—**15 mg.** three times daily.

Belladonna Leaf Fluidextract

Belladonna Leaf Fluidextract contains, in each 100 ml., not less than 270 mg. and not more than 330 mg. of the alkaloids of belladonna leaf.

Belladonna Leaf, in moderately coarse powder........... **1000 g.**

Prepare the Fluidextract from belladonna leaf by Process A, as modified for assayed fluidextracts, page 829, or by Process E, page 831.

By Process A, use a mixture of 3 volumes of alcohol and 1 volume of water as the menstruum, macerate the drug during 48 hours, and percolate at a moderate rate.

By Process E, use a mixture of 2 volumes of alcohol and 1 volume of water as the menstruum and proceed as follows: Mix 1000 g. of ground drug with 400 ml. of the menstruum, so that it is evenly and distinctly damp. Allow the dampened drug to stand for about 1 hour, then pack into a cylindrical percolator, or a series of such percolators joined together, with a length equal to about 30 times the diameter. Saturate the drug at a slow rate by forcing the menstruum under 6 to 15 pounds of air pressure through the packed drug. Allow to macerate during 48 hours, and proceed with percolation by forcing the menstruum through under pressure at a rate of about 1.5 ml. per minute until 950 ml. has been collected.

Adjust the concentrated fluid to contain, in each 100 ml., 300 mg. of the alkaloids of belladonna, and 60 percent of C_2H_5OH.

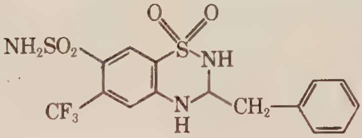
Assay—Transfer 10.0 ml. of Belladonna Leaf Fluidextract to a separator containing 25 ml. of chloroform. Add 25 ml. of water and render the mixture alkaline by the addition of ammonia T.S. Shake the mixture vigorously for about 1 minute, separate the chloroform layer, and complete the extraction of the alkaloids with successive portions of chloroform. Completely remove the alkaloids from the immiscible solvent by extracting with successive portions of approximately 0.5 *N* sulfuric acid (see *Purification of the Alkaloids* under *Proximate Assays*, page 774), filtering each portion drawn off. Render the combined acid solutions distinctly alkaline with ammonia T.S., and completely remove the alkaloids at once by extracting with successive portions of chloroform. Evaporate the combined chloroform extracts to dryness on a steam bath and keep the dry residue at this temperature for 15 minutes. Again dissolve the residue in chloroform, evaporate to dryness on a steam bath, and continue the heating for 15 minutes. Dissolve, evaporate, and heat for the third time. Dissolve the resulting residue in a few ml. of chloroform, add 15.0 ml. of 0.02 *N* sulfuric acid, remove the chloroform by evaporation, cool, add 3 drops of methyl red T.S., and titrate the excess acid with 0.02 *N* sodium hydroxide. Each ml. of 0.02 *N* sulfuric acid is equivalent to 5.788 mg. of the alkaloids of belladonna leaf.

Alcohol content, page 772—Belladonna Leaf Fluidextract contains from 57 to 63 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Belladonna Leaf Fluidextract in tight, light-resistant containers and avoid exposure to direct sunlight or to excessive heat.

CATEGORY—Anticholinergic.
USUAL DOSE—**0.06 ml.** three times a day.

Bendroflumethiazide



3-Benzyl-3,4-dihydro-6-(trifluoromethyl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide

$C_{15}H_{14}F_3N_3O_4S_2$ Mol. wt. 421.42

Bendroflumethiazide contains not less than 98.0 percent and not more than 102.0 percent of $C_{15}H_{14}F_3N_3O_4S_2$, calculated on the anhydrous basis.

Description—Bendroflumethiazide occurs as a white to cream colored, finely divided, crystalline powder. It is odorless or has a slight odor. It melts at about 220°.

Solubility—Bendroflumethiazide is practically insoluble in water. It is freely soluble in alcohol and in acetone.

Identification—Mix 5 ml. of dilute hydrochloric acid (1 in 2) with 20 mg. of Bendroflumethiazide, boil gently for 1 minute, and cool in an ice bath. Add in succession 0.5 ml. of sodium nitrite solution (1 in 1000), 0.5 ml. of ammonium sulfamate solution (1 in 200), and 0.5 ml. of *N*-(1-naphthyl)ethylenediamine dihydrochloride solution (1 in 1000): a deep red color is produced.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Bendroflumethiazide, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Bendroflumethiazide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Bendroflumethiazide in methanol exhibits maxima and minima at the same wavelengths as that of NF Bendroflumethiazide Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance occurring at about 271 mμ, do not differ by more than 4 percent.

Water, page 900—Determine the water content of Bendroflumethiazide by the titrimetric method: not more than 0.5 percent is found.

Residue on ignition, page 858—Bendroflumethiazide yields not more than 0.2 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Bendroflumethiazide is 20 parts per million.

Selenium—A *Test Preparation* prepared with 100 mg. of Bendroflumethiazide and 100 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Diazotizable substances—

Standard preparation—Weigh accurately 50.0 mg. of NF 2,4-Disulfamoyl-5-trifluoromethylaniline Reference Standard, dissolve it in sufficient methanol to make 100.0 ml., and mix. Pipet 6.0 ml. of the solution into a 100-ml. volumetric flask, dilute to volume with methanol, and mix.

Test preparation—Dissolve 100.0 mg. of Bendroflumethiazide, accurately weighed, in sufficient methanol to make 50.0 ml., and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 50-ml. volumetric flasks, and transfer 5.0 ml. of water to a third 50-ml. volumetric flask to serve as a blank. To each flask add 1.0 ml. of freshly prepared sodium nitrite solution (1 in 100) and 2.0 ml. of 1 *N* hydrochloric acid, mix, and allow to stand for 3 minutes. Add 2.0 ml. of ammonium sulfamate solution (1 in 10) to each flask, and allow to stand for 5 minutes with frequent swirling. Add 1.0 ml. of freshly prepared *N*-(1-naphthyl)ethylenediamine dihydrochloride solution (1 in 50), dilute to volume with water, and mix. Concomitantly determine the absorbances of the solutions obtained from the *Standard preparation* and *Test preparation*, in 1-cm. cells, at 520 mμ, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance of the solution from the *Test preparation* does not exceed that from the *Standard preparation*, corresponding to not more than 1.5 percent of diazotizable substances.

Assay—Dissolve about 320 mg. of Bendroflumethiazide, accurately weighed, in 25 ml. of dimethylformamide, and add 4 drops of a mixed indicator, prepared by dissolving 20 mg. of thymol blue and 5 mg. of quinaldine red in 10 ml. of methanol and diluting to 50 ml. with benzene. Titrate with 0.1 *N* lithium methoxide to a clear blue end-point, maintaining a gentle flushing with nitrogen during the titration. [Note—In conducting the titration, immediately add about 6 ml. of the titrant, and then approach the end-point at a rate of 1 to 2 drops per second.] Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* lithium methoxide is equivalent to 42.14 mg. of $C_{15}H_{14}F_3N_3O_4S_2$.

Packaging and storage—Preserve Bendroflumethiazide in tight containers.

Category—Diuretic; antihypertensive.

Usual dose range—Diuretic: Initial, **5** to **20 mg.** daily; maintenance, **2.5** to **5 mg.** daily. Antihypertensive; initial, **5** to **20 mg.** daily; maintenance, **2.5** to **15 mg.** daily.

Bendroflumethiazide Tablets

Bendroflumethiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{14}F_3N_3O_4S_2$.

Identification—The solution prepared from Bendroflumethiazide Tablets as directed in the *Content uniformity test* exhibits an ultraviolet absorption maximum at 271 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Bendroflumethiazide Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Bendroflumethiazide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer one finely powdered tablet to a 125-ml. glass-stoppered conical flask, add 50.0 ml. of acetone, insert a small funnel in the mouth of the flask, and heat on a steam bath for 3 minutes. Cool, stopper, and shake for 15 minutes. Centrifuge, and transfer a 5.0-ml. portion of the supernatant liquid to a 125-ml. conical flask. Evaporate to dryness on a steam bath, and dissolve the residue in sufficient methanol, accurately measured, to provide a concentration of 10 mcg. of bendroflumethiazide per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Bendroflumethiazide Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 271 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{15}H_{14}F_3N_3O_4S_2$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of bendroflumethiazide in the tablet; D is the exact concentration, in mcg. per ml., of bendroflumethiazide in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—

Standard preparation—Weigh accurately about 50 mg. of NF Bendroflumethiazide Reference Standard, transfer to a 100-ml. volumetric flask, dissolve in 75 ml. of 0.1 *N* sodium hydroxide, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Weigh and finely powder not less than 20 Bendroflumethiazide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg. of bendroflumethiazide, to a 100-ml. volumetric flask, add 50 ml. of 0.1 *N* sodium hydroxide, and shake well for 5 minutes. Dilute to volume with 0.1 *N* sodium hydroxide, mix, and centrifuge a 30-ml. aliquot for 15 minutes at high speed. Use the clear, supernatant liquid as directed in the *Procedure*.

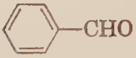
Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Assay preparation*, to separate 50-ml. volumetric flasks, and transfer 5.0 ml. of 0.1 *N* sodium hydroxide to a third flask to serve as the blank. To each flask add 25 ml. of 0.1 *N* sodium hydroxide and 5.0 ml. of dilute hydrochloric acid (1 in 2), swirl, heat in a boiling water bath for 15 minutes, and cool for 10 minutes in an ice bath. Add 3.0 ml. of sodium nitrite solution (1 in 1000), wash the neck of each flask with 1 ml. of water, swirl, and allow to stand for 3 minutes. Add 3.0 ml. of ammonium sulfamate solution (1 in 200), wash the neck of each flask with 1 ml. of water, swirl, and allow to stand for 2 minutes. Add 3.0 ml. of *N*-(1-naphthyl)ethylenediamine dihydrochloride solution (1 in 1000), dilute to volume with water, and mix. Allow to stand for not less than 10 minutes and not more than 30 minutes, and then concomitantly determine the absorbances of the solutions obtained from the *Standard preparation* and the *Assay preparation* at 515 mμ, in 1-cm. cells with a suitable spectrophotometer, using the reagent blank in the reference cell. Calculate the quantity, in mg., of $C_{15}H_{14}F_3N_3O_4S_2$ in the portion of the Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Bendroflumethiazide Reference Standard in the *Standard preparation*, and A_U and A_S are the absorbances of the solutions obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Packaging and storage—Preserve Bendroflumethiazide Tablets in tight containers.

Tablets available—Bendroflumethiazide Tablets usually available contain the following amounts of bendroflumethiazide: 2.5 mg. and 5 mg.

CATEGORY and DOSE—See Bendroflumethiazide.

Benzaldehyde



C_7H_6O Mol. wt. 106.13

Benzaldehyde contains not less than 98.0 percent and not more than 100.5 percent of C_7H_6O.

Description—Benzaldehyde is a colorless, strongly refractive liquid, having an odor resembling that of bitter almond oil, and a burning, aromatic taste. It is affected by light.

Solubility—Benzaldehyde is slightly soluble in water, and is miscible with alcohol, with ether, with fixed and with volatile oils.

Specific gravity, page 866—The specific gravity of Benzaldehyde is not less than 1.041 and not more than 1.046.

Refractive index, page 858—The refractive index of Benzaldehyde is not less than 1.544 and not more than 1.546 at 20°.

Hydrocyanic acid—Shake 0.5 ml. of Benzaldehyde with 5 ml. of water, add 0.5 ml. of sodium hydroxide T.S. and 0.1 ml. of ferrous sulfate T.S., and warm the mixture gently. Upon the addition of a slight excess of hydrochloric acid, no greenish blue color or blue precipitate is produced within 15 minutes.

Chlorinated compounds—Wind a strip of 20 mesh copper gauze 1.5 cm. wide and 5 cm. long around the end of a copper wire. Heat the gauze in the nonluminous flame of a Bunsen burner until it glows without coloring the flame green. Permit the gauze to cool and reheat several times until a good coat of oxide has formed. Apply with a medicine dropper, 2 drops of Benzaldehyde to the cooled gauze, ignite, and permit it to burn freely in the air. Again cool the gauze and add 2 more drops of Benzaldehyde and burn as before. This process is continued until a total of 6 drops has been added and ignited. Then hold the gauze in the outer edge of the Bunsen flame, adjusted to a height of about 4 cm.: not even a transient green color is imparted to the flame.

Nitrobenzene—Dissolve 1 ml. of Benzaldehyde in 20 ml. of alcohol and add water until a slight turbidity is produced. Add zinc and diluted sulfuric acid, maintaining a brisk evolution of hydrogen for 1 hour. Filter, evaporate the liquid to about 20 ml., and boil 10 ml. of the concentrated liquid with 1 drop of potassium dichromate T.S.: no purplish color is produced.

Assay—Transfer about 1 ml. of Benzaldehyde to a tared glass-stoppered weighing bottle, and weigh accurately. Loosen the stopper and transfer the weighing bottle and contents to a 250-ml. conical flask containing 25 ml. of a reagent prepared by dissolving 34.7 g. of hydroxylamine hydrochloride in 160 ml. of water and diluting this solution to 1000 ml. with alcohol. Rinse down the sides of the flask with an additional 50 ml. of the reagent. Allow to stand for 10 minutes, add 1 ml. of bromophenol blue T.S., and titrate the liberated hydrochloric acid with 1 *N* sodium hydroxide to a light green end-point. Perform a blank determination (see *Residual Titrations,* page 883), titrating to the same color as in the assay determination. To determine the number of ml. of 1 *N* sodium hydroxide required to neutralize the liberated hydrochloric acid, subtract the number of ml. of 1 *N* sodium hydroxide used in the blank from the number of ml. required in the assay. Each ml. of 1 *N* sodium hydroxide is equivalent to 106.1 mg. of C_7H_6O.

Packaging and storage—Preserve Benzaldehyde in well-filled, tight, light-resistant containers.

CATEGORY—Flavor.

Compound Benzaldehyde Elixir

Benzaldehyde	0.5	ml.
Vanillin	1	g.
Orange Flower Water	150	ml.
Alcohol	50	ml.
Syrup	400	ml.
Purified Water, a sufficient quantity,		
To make	1000	ml.

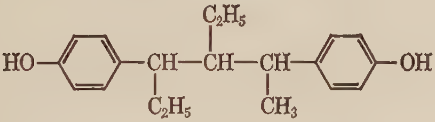
Dissolve the benzaldehyde and the vanillin in the alcohol; add the syrup, the orange flower water, and sufficient purified water, in several portions, shaking the mixture thoroughly after each addition, to make the product measure 1000 ml.; then filter, if necessary, until the product is clear.

Alcohol content, page 772—Compound Benzaldehyde Elixir contains from 3 to 5 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Compound Benzaldehyde Elixir in tight, light-resistant containers.

CATEGORY—Vehicle.

Benzestrol



4,4′-(1,2-Diethyl-3-methyltrimethylene)diphenol

$C_{20}H_{26}O_2$ Mol. wt. 298.43

Benzestrol, dried at 105° for 1 hour, contains not less than 98.5 percent and not more than 100.5 percent of $C_{20}H_{26}O_2$.

Description—Benzestrol occurs as a white, crystalline powder. A solution of Benzestrol in ether (1 in 50) is clear and colorless. A 1 in 50 solution of Benzestrol in previously neutralized 80 percent alcohol is neutral to litmus.

Solubility—Benzestrol is practically insoluble in water and in dilute mineral acids. It is freely soluble in acetone, in alcohol, in ether, in methanol, and in sodium hydroxide T.S. It is soluble in vegetable oils, moderately soluble in glacial acetic acid, and slightly soluble in diluted alcohol, in benzene, in chloroform, and in solvent hexane.

Identification—

A: Dissolve about 10 mg. of Benzestrol in 2 ml. of sulfuric acid: a pale yellow color is produced which persists on dilution with water (*distinction from diethylstilbestrol, which yields an orange color*).

B: Add a few drops of a solution of antimony pentachloride in dry, alcohol-free chloroform (1 in 2) to a very dilute solution of Benzestrol in the same solvent: a green colored solution is produced which rapidly changes to brown (*distinction from diethylstilbestrol, which yields a red to bluish red color*).

C: Add 1 ml. of benzoyl chloride to 100 mg. of Benzestrol in a test tube. Boil gently for 5 minutes, cool, add 20 ml. of sodium hydroxide T.S., and shake until a white, solid mass separates. Filter, wash the precipitate with water, recrystallize it twice from hot alcohol, and dry at 80° for 30 minutes: the 2,4-bis(*p*-hydroxyphenyl)-3-ethylhexane dibenzoate so obtained melts between 118° and 120°, page 814.

Melting range, page 814—Benzestrol melts between 161° and 163°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Benzestrol, previously dried at 105° for 1 hour, exhibits maxima only at the same wavelengths as that of NF Benzestrol Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Benzestrol in alcohol exhibits maxima and minima at the same wavelengths as that of NF Benzestrol Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 278 mμ, do not differ by more than 2.5 percent.

Loss on drying, page 814—Dry Benzestrol at 105° for 1 hour: it loses not more than 0.1 percent of its weight.

Residue on ignition, page 858—Benzestrol yields not more than 0.05 percent of residue on ignition.

Assay—

Standard preparation—Weigh accurately about 100 mg. of NF Benzestrol Reference Standard, previously dried at 105° for 1 hour, dissolve it in sufficient alcohol to make 100.0 ml., and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix.

Assay preparation—Weigh accurately about 100 mg. of Benzestrol, previously dried at 105° for 1 hour, dissolve it in sufficient alcohol to make 100.0 ml., and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix.

Procedure—Pipet 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate 50-ml. volumetric flasks. To each flask add 2.0 ml. of diluted hydrochloric acid and 4.0 ml. of molybdophosphotungstate T.S., and mix. Let the flasks stand for 10 minutes, then add 10.0 ml. of sodium carbonate solution (1 in 4), add water to volume, and mix. Let the flasks stand for an hour, then centrifuge. Determine the absorbances of the clear, supernatant solutions in 1-cm. cells, at 750 mμ, with a suitable spectrophotometer, using as the blank a solution prepared from the same quantities of the same reagents and in the same manner. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{20}H_{26}O_2$ in the Benzestrol taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Benzestrol in tight containers.

CATEGORY—Estrogen.
USUAL DOSE—Oral, **1** to **2 mg.** daily.
USUAL DOSE RANGE—**500 mcg.** to **5 mg.**

Benzestrol Tablets

Benzestrol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{26}O_2$.

Identification—Benzestrol, obtained as directed in the *Assay preparation,* responds to the *Identification tests* under *Benzestrol,* page 75.

Disintegration, page 878—The disintegration time limit for Benzestrol Tablets is 15 minutes.

Content uniformity, *Method I,* page 799—Benzestrol Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Benzestrol,* page 75.

Assay preparation—Weigh and finely powder not less than 20 Benzestrol Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg. of benzestrol, to a separator containing 30 ml. of water and 2 drops of hydrochloric acid, and extract with five 20-ml. portions of peroxide-free ether. Extract the combined ether extracts with one 25-ml. portion and three 15-ml. portions of sodium hydroxide T.S., and discard the ether solution. Acidify the combined sodium hydroxide extracts with diluted sulfuric acid, and extract with five 25-ml. portions of peroxide-free ether. Filter the combined ether extracts through peroxide-free, ether-washed cotton, wash the cotton with several small portions of the ether, and evaporate the ether by gentle warming. Dissolve the residue in 20 ml. of alcohol, transfer to a 100-ml. volumetric flask with the aid of alcohol, dilute to volume with alcohol, and mix.

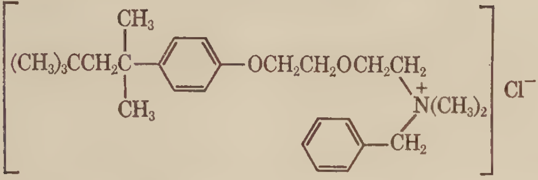
Procedure—Proceed as directed in the *Procedure* in the *Assay* under *Benzestrol,* page 75, beginning with "Pipet 5.0 ml. each. . . ." Calculate the quantity, in mg., of $C_{20}H_{26}O_2$ in the portion of the Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Benzestrol Reference Standard in the *Standard preparation.*

Packaging and storage—Preserve Benzestrol Tablets in tight containers.

Tablets available—Benzestrol Tablets usually available contain the following amounts of benzestrol: 1, 2, and 5 mg.

CATEGORY AND DOSE—See Benzestrol.

Benzethonium Chloride



Benzyldimethyl[2-[2-[*p*-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]ammonium Chloride

$C_{27}H_{42}ClNO_2$ Mol. wt. 448.09

Benzethonium Chloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{27}H_{42}ClNO_2$, calculated on the dried basis.

Description—Benzethonium Chloride occurs as colorless crystals. It has a mild odor and has a very bitter taste. Its 1 in 100 solution is slightly alkaline to litmus.

Solubility—Benzethonium Chloride is soluble in water, in alcohol, and in chloroform. It is only slightly soluble in ether.

Identification—

A: To 1 ml. of a solution of Benzethonium Chloride (1 in 100) add 2 ml. of alcohol, 0.5 ml. of diluted nitric acid and 1 ml. of silver nitrate T.S.: a white precipitate, which is insoluble in diluted nitric acid but soluble in diluted ammonia solution, is formed.

B: A solution of Benzethonium Chloride (1 in 100) forms precipitates with diluted nitric acid and with mercuric chloride T.S., both of which dissolve upon the addition of alcohol.

C: Dissolve 100 mg. of Benzethonium Chloride in 1 ml. of sulfuric acid, add 100 mg. of potassium nitrate, and heat on a steam bath for 3 minutes. Cautiously dilute the solution with water to 10 ml., add 500 mg. of granulated zinc, and warm the mixture for 10 minutes. Cool, add 200 mg. of sodium nitrite to 1 ml. of the clear liquid, and add this mixture to 20 mg. of naphthol sodium disulfonate in 1 ml. of stronger ammonia water: the solution turns orange-red and a brown precipitate may appear.

Melting range, page 814—Benzethonium Chloride, dried at 105° for 4 hours, melts between 158° and 163°.

Loss on drying, page 814—Dry Benzethonium Chloride at 105° for 4 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Benzethonium Chloride yields not more than 0.1 percent of residue on ignition.

Ammonium compounds—To 5 ml. of a solution of Benzethonium Chloride (1 in 50) add 3 ml. of sodium hydroxide T.S., and heat to boiling: the odor of ammonia is not perceptible.

Assay—Dissolve about 300 mg. of Benzethonium Chloride, accurately weighed, in 75 ml. of water contained in a glass-stoppered, 250-ml. flask. Add 0.4 ml. of bromophenol blue solution (1 in 2000), 10 ml. of chloroform, and 1 ml. of sodium hydroxide T.S. Titrate with 0.02 *M* sodium tetraphenylboron until the blue color disappears from the chloroform layer. Add the last portions of the sodium tetraphenylboron solution dropwise, agitating vigorously after each addition. Each ml. of 0.02 *M* sodium tetraphenylboron is equivalent to 8.962 mg. of $C_{27}H_{42}ClNO_2$.

Packaging and storage—Preserve Benzethonium Chloride in tight, light-resistant containers.

CATEGORY—Local anti-infective.

APPLICATION—Topical, as a 1:750 solution to the skin or 1:5000 solution nasally.

Benzethonium Chloride Solution

Benzethonium Chloride Solution contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{27}H_{42}ClNO_2$.

Description—Benzethonium Chloride Solution is odorless and has a bitter taste. It is slightly alkaline to litmus.

Identification—The residue obtained by evaporating, on a steam bath, a volume of Benzethonium Chloride Solution equivalent to about 200 mg. of benzethonium chloride, responds to the *Identification* *tests* under *Benzethonium Chloride,* page 77.

Oxidizing substances—To 5 ml. of Benzethonium Chloride Solution add 0.5 ml. of potassium iodide T.S. and a few drops of diluted hydrochloric acid: the solution does not acquire a yellow color.

Nitrites—To 1 drop of Benzethonium Chloride Solution on a spot plate, add 1 drop each of glacial acetic acid, sulfanilic acid in acetic acid (1 in 100), and α-naphthylamine-acetic acid solution (prepared by boiling 30 mg. of α-naphthylamine in 70 ml. of water, decanting the colorless solution from the blue-violet residue, and mixing with 30 ml. of glacial acetic acid): no red color develops in the resulting solution within 10 minutes.

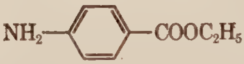
Assay—Pipet into a glass-stoppered flask a volume of Benzethonium Chloride Solution, equivalent to about 200 mg. of benzethonium chloride, and proceed as directed in the *Assay* under *Benzethonium Chloride,* page 77, beginning with "Add 0.4 ml. of bromophenol blue solution (1 in 2000) . . ."

Packaging and storage—Preserve Benzethonium Chloride Solution in tight, light-resistant containers.

Solutions available—Benzethonium Chloride Solution is usually available in the following concentrations: 1:750 and 3 percent.

Category and Application—See Benzethonium Chloride.

Benzocaine



Ethyl *p*-Aminobenzoate

$C_9H_{11}NO_2$ Mol. wt. 165.19

Benzocaine, dried over phosphorus pentoxide for 3 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_9H_{11}NO_2$.

Description—Benzocaine occurs as small, white crystals, or as a white, crystalline powder. It is odorless, and is stable in air. Benzocaine exhibits local anesthetic properties when placed upon the tongue.

Solubility—Benzocaine is very slightly soluble in water. It is freely soluble in alcohol, in chloroform, and in ether, and is sparingly soluble in almond oil or olive oil. It dissolves in dilute acids.

Identification—

A: Boil Benzocaine with sodium hydroxide T.S.: alcohol, recognizable by its odor, is produced.

B: Dissolve about 20 mg. of Benzocaine in 10 ml. of water with the aid of a few drops of diluted hydrochloric acid, and add 5 drops of a solution of sodium nitrite (1 in 10), followed by 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S.: an orange-red precipitate is formed.

C: To a solution of Benzocaine (1 in 50), prepared with the aid of a slight excess of diluted hydrochloric acid, add iodine T.S.: a precipitate is formed.

Melting range, page 814—Benzocaine melts, within a 2° range, between 88° and 92°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Benzocaine, previously dried over phosphorus pentoxide for 3 hours, exhibits maxima only at the same wavelengths as that of NF Benzocaine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Benzocaine in chloroform exhibits maxima and minima at the same wavelengths as that of NF Benzocaine Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 292 mμ, do not differ by more than 3 percent.

Reaction—Dissolve 1 g. of Benzocaine in 10 ml. of neutralized alcohol: a clear solution results. Dilute this solution with 10 ml. of water, and add 2 drops of phenolphthalein T.S. and 1 drop of 0.1 *N* sodium hydroxide: a red color is produced.

Loss on drying, page 814—Dry Benzocaine over phosphorus pentoxide for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Benzocaine yields not more than 0.1 percent of residue on ignition.

Chloride—To a solution of 200 mg. of Benzocaine in 5 ml. of alcohol, previously acidified with a few drops of diluted nitric acid, add a few drops of silver nitrate T.S.: no turbidity is produced immediately.

Heavy metals, *Method II*, page 806—The heavy metals limit for Benzocaine is 10 parts per million.

Readily carbonizable substances, page 856—Dissolve 500 mg. of Benzocaine in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid A.

Assay—Dissolve about 300 mg. of Benzocaine, previously dried over phosphorus pentoxide for 3 hours and accurately weighed, in a mixture of 100 ml. of water and 15 ml. of hydrochloric acid. Cool the solution in an ice bath to about 10°, and titrate with 0.1 *M* sodium nitrite until a blue color is produced immediately when the titrated solution is spotted on starch iodide paper. When the titration is complete, the end-point is reproducible after the mixture has been allowed to stand for 5 minutes. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 16.52 mg. of $C_9H_{11}NO_2$.

Packaging and storage—Preserve Benzocaine in well-closed containers.

CATEGORY—Local anesthetic.

APPLICATION—Topical, as a 1 to 20 percent ointment to the skin.

Benzocaine Ointment

Benzocaine Ointment contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{11}NO_2$ in a suitable ointment base.

Identification—

Ointments having water-soluble bases—Transfer an amount of Benzocaine Ointment, equivalent to about 5 mg. of benzocaine, into a small beaker, add 20 ml. of 0.5 *N* hydrochloric acid, warm gently to disperse the ointment, cool, and filter if necessary. To 10 ml. of the filtrate add 5 drops of a solution of sodium nitrite (1 in 10) and 2 drops of methyl red T.S., and neutralize with sodium hydroxide T.S. Add 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S.: an orange-red precipitate is formed.

Ointments having water-insoluble bases—Transfer an amount of Benzocaine Ointment, equivalent to about 2.5 mg. of benzocaine, into a small separator and dissolve in 20 ml. of ether. Extract with 10 ml. of 0.5 *N* hydrochloric acid and filter the aqueous phase through paper into a small beaker. Add 5 drops of a solution of sodium nitrite (1 in 10) and 2 drops of methyl red T.S., and neutralize with sodium hydroxide T.S. Add 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S.: an orange-red precipitate is formed.

Assay—

Ointments having water-soluble bases—Weigh accurately an amount of Benzocaine Ointment, equivalent to about 200 mg. of benzocaine, in a tared 250-ml. beaker. Add 50 ml. of water and 5 ml. of hydrochloric acid, and stir mechanically until solution is effected. Cool the solution in an ice bath to about 10°, and titrate slowly with 0.1 *M* sodium nitrite, determining the end-point electrometrically, using calomel and platinum electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 16.52 mg. of $C_9H_{11}NO_2$.

Ointments having water-insoluble bases—Weigh accurately an amount of Benzocaine Ointment, equivalent to about 200 mg. of benzocaine, and transfer to a 125-ml. separator. Suspend the ointment in 50 ml. of ether by shaking, and extract with three successive 25-ml. portions of 1 *N* hydrochloric acid, filtering each portion into a 250-ml. beaker, and proceed as directed under *Ointments having water-soluble bases* beginning with "Cool the solution. . . ."

Packaging and storage—Preserve Benzocaine Ointment in tight containers protected from light, and avoid prolonged exposure to temperatures above 30°.

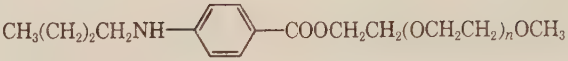
Ointments available—Benzocaine Ointment usually available contains 1, 2.5, 5, 10, and 20 percent of benzocaine.

CATEGORY AND APPLICATION—See Benzocaine.

Benzocaine and Antipyrine Solution, page 60

Benzocaine and Trimethobenzamide Hydrochloride Suppositories, page 739

Benzonatate*



2,5,8,11,14,17,20,23,26-Nonaoxaoctacosan-28-yl *p*-(Butylamino)benzoate

$C_{30}H_{53}NO_{11}$ (av.) Mol. wt. (av.) 603

Benzonatate contains not less than 95.0 percent and not more than 105.0 percent of $C_{30}H_{53}NO_{11}$.

Description—Benzonatate occurs as a clear, pale yellow, viscous liquid having a faint, characteristic odor. Benzonatate has a bitter taste and exhibits local anesthetic properties when placed upon the tongue.

Solubility—Benzonatate is miscible with water in all proportions. It is freely soluble in chloroform, in alcohol, and in benzene.

Identification—Reflux about 2 g. of Benzonatate with 10 ml. of water and 20 ml. of 0.5 *N* sodium hydroxide for about 3 hours. Neutralize the solution to congo red with 0.5 *N* hydrochloric acid, filter, wash the precipitate with a small amount of cold water, and dry the crystals at 105° for 2 hours: the *p*-(butylamino)benzoic acid so obtained melts between 150° and 153°, page 814.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 67,000 solution of Benzonatate in water exhibits maxima and minima at the same wavelengths as that of NF Benzonatate Reference Standard, similarly measured.

Refractive index, page 858—The refractive index of Benzonatate, determined at 20°, is not less than 1.509 and not more than 1.511.

Water, page 900—Determine the water content of Benzonatate by the titrimetric method: not more than 0.3 percent is found.

Residue on ignition, page 858—Benzonatate yields not more than 0.1 percent of residue on ignition.

Arsenic—A *Test Preparation* prepared with 6.67 g. of Benzonatate, as directed for organic compounds, meets the requirements of the *Arsenic Test,* page 777 (1.5 parts per million As).

Chloride—To 20 ml. of a 1 in 20 solution of Benzonatate, add 1 ml. of nitric acid and 1 ml. of silver nitrate T.S. Dilute to 50 ml. with water, mix, and allow to stand protected from light for 10 minutes: no turbidity is produced.

Sulfate—To 5 ml. of a 1 in 20 solution of Benzonatate, add 5 ml. of water, 1 ml. of dilute hydrochloric acid, and 1 ml. of barium chloride T.S. Mix, and allow to stand for 10 minutes: no turbidity is produced.

Heavy metals, *Method II,* page 806—The heavy metals limit for Benzonatate is 10 parts per million.

Assay—Weigh accurately about 5 g. of Benzonatate, and reflux for 1 hour with 25.0 ml. of 0.5 *N* sodium hydroxide. Cool, add 25 ml. of water and 10 drops of bromothymol blue T.S., and titrate the excess alkali with 0.5 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 0.5 *N* sodium hydroxide is equivalent to 301.5 mg. of $C_{30}H_{53}NO_{11}$.

Packaging and storage—Preserve Benzonatate in tight, light-resistant containers.

CATEGORY—Antitussive.
USUAL DOSE—**100 mg.** three times a day.
USUAL DOSE RANGE—**100** to **200 mg.**

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* Patented. See notice, page ii.

Benzonatate Capsules

Benzonatate Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of benzonatate ($C_{30}H_{53}NO_{11}$ av.).

Identification—

A: Empty several Benzonatate Capsules, equivalent to about 2 g. of benzonatate, and reflux with 10 ml. of water and 20 ml. of sodium hydroxide T.S. for about 3 hours. Neutralize to congo red with 0.5 *N* hydrochloric acid, filter, wash the precipitate with a small amount of cold water, and dry the crystals at 105° for 2 hours: the *p*-(butylamino)benzoic acid so obtained melts between 150° and 153°, page 814.

B: The contents of Benzonatate Capsules meet the requirements of the test for *Ultraviolet absorption* under *Benzonatate,* page 80.

Content uniformity, *Method I,* page 798—Benzonatate Capsules meet the requirements of the content uniformity test for capsules.

Assay—

Standard preparation—Transfer about 50 mg. of NF Benzonatate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix.

Assay preparation—Mix a number of Benzonatate Capsules, equivalent to about 500 mg. of benzonatate, with 40 ml. of chloroform in a suitable high speed blending apparatus, and dilute to 50.0 ml. with chloroform. Transfer 5.0 ml. of this solution, equivalent to about 50 mg. of benzonatate, to a 100-ml. volumetric flask, and evaporate the chloroform on a steam bath with the aid of a current of air. Dissolve the residue in water, dilute to volume with water, and mix.

Procedure—Transfer 4.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of water to separate test tubes. To each tube add in succession 1.0 ml. of 1 *M* hydroxylamine hydrochloride and 1.0 ml. of 3.5 *M* sodium hydroxide, mixing well after each addition. Allow to stand for exactly 10 minutes, then add 1.0 ml. of 3.5 *M* hydrochloric acid, mix, add 1.0 ml. of 0.3 *M* ferric chloride, and mix. Allow to stand for exactly 30 minutes, and pass a stream of air through the solution to remove gas bubbles. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 500 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of benzonatate ($C_{30}H_{53}NO_{11}$ av.) in the number of Capsules taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

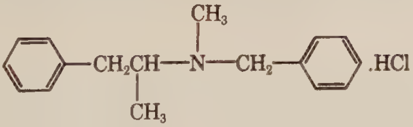
Packaging and storage—Preserve Benzonatate Capsules in tight, light-resistant containers.

Capsules available—Benzonatate Capsules usually available contain the following amounts of benzonatate: 50 and 100 mg.

CATEGORY and DOSE—See Benzonatate.

Benzoylpas, Calcium, page 116
Benzoylpas, Calcium, Tablets, page 117

Benzphetamine Hydrochloride



(+)-*N*-Benzyl-*N*,α-dimethylphenethylamine Hydrochloride

$C_{17}H_{21}N.HCl$ Mol. wt. 275.82

Benzphetamine Hydrochloride contains not less than 98.0 percent and not more than 101.0 percent of $C_{17}H_{21}N.HCl$, calculated on the dried basis.

Description — Benzphetamine Hydrochloride occurs as an odorless, white to off-white, crystalline powder.

Solubility—Benzphetamine Hydrochloride is freely soluble in water, in alcohol, and in chloroform. It is slightly soluble in ether.

Identification—

A: To a solution of Benzphetamine Hydrochloride (1 in 100) add picric acid T.S.: a yellow precipitate is formed which is soluble in alcohol.

B: A solution of Benzphetamine Hydrochloride (1 in 100) responds to the test for *Chloride*, page 808.

Melting range, page 814—Benzphetamine Hydrochloride melts between 152° and 158°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Benzphetamine Hydrochloride, previously dried in vacuum at 60° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Benzphetamine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 1000 solution of Benzphetamine Hydrochloride in alcohol exhibits maxima and minima at the same wavelengths as that of NF Benzphetamine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about

258 mμ, do not differ by more than 2.5 percent.

Specific rotation, page 822—The specific rotation of Benzphetamine Hydrochloride, calculated on the dried basis, determined in a solution in water containing 200 mg. of Benzphetamine Hydrochloride in each 10 ml., is between +22° and +26°.

Loss on drying, page 814—Dry Benzphetamine Hydrochloride in vacuum at 60° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Benzphetamine Hydrochloride yields not more than 0.2 percent of residue on ignition.

Methamphetamine hydrochloride—

Standard preparation—Weigh accurately about 30 mg. of USP Methamphetamine Hydrochloride Reference Standard and dissolve in sufficient water to make 200.0 ml. Transfer 1.0 ml. of this solution to a glass-stoppered 30-ml. tube.

Test preparation—Transfer about 20 mg. of Benzphetamine Hydrochloride, accurately weighed, to a glass-stoppered 30-ml. tube, and dissolve in 1.0 ml. of water.

Procedure—To the *Standard preparation,* to the *Test preparation,* and to a third glass-stoppered 30-ml. tube containing 1.0 ml. of water to serve as the blank, add 4.0 ml. of a freshly prepared mixture of 35 ml. of carbon disulfide, 25 ml. of pyridine, and 65 ml. of isopropyl alcohol, and then add 2.0 ml. of a solution prepared by dissolving 300 mg. of cupric sulfate ($CuSO_4.5H_2O$) in 250 ml. of water and diluting to 500 ml. with pyridine. Mix the contents of the tubes by swirling, and allow to stand for 10 minutes. To each tube add 3.0 ml. of dilute acetic acid (1 in 20) and 3.0 ml. of benzene. Shake the tubes, allow the layers to separate, and transfer the benzene layers to separate 10-ml. flasks, each containing 300 mg. of anhydrous sodium sulfate. Concomitantly determine the absorbance of each solution in 1-cm. cells, at the maximum at about 445 mμ, with a suitable spectrophotometer, using the blank to set the instrument. The absorbance of the solution from the *Test preparation* does not exceed that from the *Standard preparation,* indicating not more than 0.75 percent of methamphetamine hydrochloride.

Assay—Dissolve about 500 mg. of Benzphetamine Hydrochloride, accurately weighed, in a mixture of 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 27.58 mg. of $C_{17}H_{21}N.HCl$.

Packaging and storage—Preserve Benzphetamine Hydrochloride in tight, light-resistant containers.

CATEGORY—Anorexiant.

USUAL DOSE RANGE—**25** to **50 mg.** one to three times daily.

Benzphetamine Hydrochloride Tablets

Benzphetamine Hydrochloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{17}H_{21}N.HCl$.

Identification—Powder a number of Benzphetamine Hydrochloride Tablets, equivalent to about 50 mg. of benzphetamine hydrochloride, and digest with 25 ml. of chloroform for 10 minutes. Filter, evaporate the filtrate to dryness, and dry at room temperature in a vacuum. The residue so obtained meets the requirements for *Infrared absorption* under *Benzphetamine Hydrochloride,* page 81.

Disintegration, page 878—The disintegration time limit for Benzphetamine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Benzphetamine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Sodium lauryl sulfate, 0.02 N—Dissolve 5.8 g. of sodium lauryl sulfate in sufficient water to make 1000.0 ml., and mix. Determine the normality of the solution as directed in the *Procedure,* using NF Benzphetamine Hydrochloride Reference Standard as the primary standard.

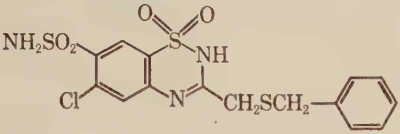
Procedure—Weigh and finely powder not less than 20 Benzphetamine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 125 mg. of benzphetamine hydrochloride, to a glass-stoppered 250-ml. conical flask with the aid of 20 ml. of water, add 4 drops of a solution of *p*-dimethylaminoazobenzene in alcohol (1 in 1000), 20 ml. of chloroform, and 5 ml. of 3 *N* sulfuric acid. Titrate with 0.02 *N* sodium lauryl sulfate, shaking vigorously after each addition of the titrant, until a red color appears in the chloroform layer. Each ml. of 0.02 *N* sodium lauryl sulfate is equivalent to 5.516 mg. of $C_{17}H_{21}N.HCl$.

Packaging and storage—Preserve Benzphetamine Hydrochloride Tablets in tight containers.

Tablets available—Benzphetamine Hydrochloride Tablets usually available contain the following amounts of benzphetamine hydrochloride: 25 and 50 mg.

Category and Dose—See Benzphetamine Hydrochloride.

Benzthiazide



3-[(Benzylthio)methyl]-6-chloro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide

$C_{15}H_{14}ClN_3O_4S_3$ Mol. wt. 431.94

Benzthiazide contains not less than 98.0 percent and not more than 101.5 percent of $C_{15}H_{14}ClN_3O_4S_3$, calculated on the dried basis.

Description—Benzthiazide occurs as a white, crystalline powder having a characteristic odor. It melts at about 242°.

Solubility—Benzthiazide is practically insoluble in water. It is freely soluble in dimethylformamide and in solutions of fixed alkali hydroxides. It is slightly soluble in acetone and practically insoluble in ether and in chloroform

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Benzthiazide, previously dried in vacuum at 65° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Benzthiazide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 62,500 solution of Benzthiazide in 0.01 *N* alcoholic hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Benzthiazide Reference Standard, similarly measured.

Loss on drying, page 814—Dry Benzthiazide in vacuum at 65° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Benzthiazide yields not more than 0.2 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 100 mg. of Benzthiazide and 100 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Heavy Metals, *Method II,* page 806—The heavy metals limit for Benzthiazide is 25 parts per million.

Diazotizable substances—

Standard preparation—Weigh accurately 10.0 mg. of NF 4-Amino-6-chloro-1,3-benzenedisulfonamide Reference Standard, and dissolve in sufficient acetone to make 50.0 ml. Pipet 4.0 ml. of the solution into a 100-ml. volumetric flask, add acetone to volume, and mix.

Test preparation—Dissolve 80.0 mg. of Benzthiazide, accurately weighed, in sufficient acetone to make 100.0 ml., and mix.

Procedure—Transfer 1.0 ml. each of the *Standard preparation* and of the *Test Preparation* to separate tubes, and transfer 1.0 ml. of acetone to a third tube to serve as a blank. To each tube add 9.0 ml. of 1 *N* hydrochloric acid and 0.1 ml. of freshly prepared sodium nitrite solution (1 in 25), mix, and allow to stand for 1 minute. Add 0.8 ml. of ammonium sulfamate solution (1 in 50), mix and allow to stand for 3 minutes. Add 0.8 ml. of a solution of *N*-1-naphthylethylenediamine dihydrochloride in 50 percent alcohol (1 in 50) to each tube, and mix. After 2 minutes, concomitantly determine the absorbances of the solutions obtained from the *Standard preparation* and *Test preparation,* in 1-cm. cells, at 518 mμ, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance of the solution from the *Test preparation* does not exceed that of the solution from the *Standard preparation,* corresponding to not more than 1.0 percent of diazotizable substances.

Assay—Transfer about 100 mg. of Benzthiazide, accurately weighed, to a 250-ml. volumetric flask, add 200 ml. of 0.01 *N* alcoholic hydrochloric acid, and stir for 1 hour to dissolve. Dilute to volume with 0.01 *N* alcoholic hydrochloric acid, and mix. Transfer 2.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with 0.01 *N* alcoholic hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Benzthiazide Reference Standard, in the same medium at a concentration of about 16 mcg. per ml., in 1-cm.

cells, at the maximum at about 289 mμ, with a suitable spectrophotometer, using 0.01 *N* alcoholic hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{15}H_{14}ClN_3O_4S_3$ in the Benzthiazide taken by the formula $6.25C \times (A_U/A_S)$, in which *C* is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Benzthiazide in tight containers.

CATEGORY—Diuretic; antihypertensive.

USUAL DOSE RANGE—Diuretic—initial, **50** to **200 mg.** daily; maintenance, **50** to **150 mg.** daily. Antihypertensive—initial, **25** to **50 mg.** twice daily; maintenance, adjust to the response of the patient with a maximal dose of **50 mg.** three times a day.

Benzthiazide Tablets

Benzthiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{14}ClN_3O_4S_3$.

Identification—The solution of benzthiazide, obtained from Benzthiazide Tablets as directed in the *Assay*, exhibits an absorbance maximum at 295 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Benzthiazide Tablets, using simulated gastric fluid T.S. as the test medium in place of water, is 30 minutes.

Content uniformity, *Method II*, page 799—Benzthiazide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask, add 1 ml. of 0.1 *N* hydrochloric acid and 50 ml. of alcohol, and heat on a steam bath for 15 minutes. Cool, dilute to volume with alcohol, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate with 0.01 *N* alcoholic hydrochloric acid to provide a solution containing approximately 20 mcg. of benzthiazide per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Benzthiazide Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 283 mμ, with a suitable spectrophotometer, using 0.01 *N* alcoholic hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{15}H_{14}ClN_3O_4S_3$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which *T* is the labeled quantity, in mg., of benzthiazide in the tablet; *D* is the exact concentration, in mcg. per ml., of benzthiazide in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; *C* is the exact concentration in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

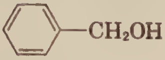
Assay—Weigh and finely powder not less than 20 Benzthiazide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of benzthiazide, to a 100-ml. volumetric flask, add 0.2 *N* sodium hydroxide to volume, and mix. Filter through fast filter paper, discarding the first 20 ml. of filtrate, and transfer 10.0 ml. of the subsequent filtrate to a separator. To the separator add 3 ml. of dilute hydrochloric acid, shake vigorously for 2 minutes, and then extract successively with one 50-ml. portion and two 25-ml. portions of ether. Evaporate the combined ether extracts to a volume of about 5 ml. on a steam bath. Add 10 ml. of 0.2 *N* sodium hydroxide while washing down the sides of the container, and continue the evaporation until all traces of ether are expelled. Cool, and dissolve the residual liquid in 0.2 *N* sodium hydroxide. Quantitatively transfer the solution to a 100-ml. volumetric flask with the aid of 0.2 *N* sodium hydroxide, dilute to volume with 0.2 *N* sodium hydroxide, and mix. Transfer 20.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with 0.2 *N* sodium hydroxide, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Benzthiazide Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 295 mμ, with a suitable spectrophotometer, using 0.2 *N* sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_{15}H_{14}ClN_3O_4S_3$ in the portion of Tablets taken by the formula $2.5C \times (A_U/A_S)$, in which *C* is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Benzthiazide Tablets in tight containers.

Tablets available—Benzthiazide Tablets usually available contain the following amount of benzthiazide: 50 mg.

CATEGORY and DOSE—See Benzthiazide.

Benzyl Alcohol



C_7H_8O Mol. wt. 108.14

Description—Benzyl Alcohol is a colorless liquid with a faint, aromatic odor and a sharp burning taste. Benzyl Alcohol boils without decomposition at about 206°. It is neutral to litmus.

Solubility—Benzyl Alcohol is sparingly soluble in water and is freely soluble in 50 percent alcohol. It is miscible with alcohol, with ether, and with chloroform.

Identification—Add 2 or 3 drops of Benzyl Alcohol to 5 ml. of a solution of potassium permanganate (1 in 20), and acidify with diluted sulfuric acid: the odor of benzaldehyde is noticeable.

Specific gravity, page 866—The specific gravity of Benzyl Alcohol is not less than 1.042 and not more than 1.047.

Distilling range, *Method II*, page 782—Not less than 94 percent, by volume, of Benzyl Alcohol distils between 202.5° and 206.5°.

Refractive index, page 858—The refractive index of Benzyl Alcohol is not less than 1.538 and not more than 1.540 at 20°.

Residue on ignition—Evaporate 10 ml. of Benzyl Alcohol in a suitable crucible and ignite to constant weight: the weight of the residue on ignition is negligible.

Chlorinated compounds—Wind a strip of 20 mesh copper gauze 1.5 cm. wide and 5 cm. long around the end of a copper wire. Heat the gauze in the nonluminous flame of a Bunsen burner until it glows without coloring the flame green. Permit the gauze to cool and re-heat several times until a good coat of oxide has formed. Apply with a medicine dropper, 2 drops of Benzyl Alcohol to the cooled gauze, ignite, and permit it to burn freely in the air. Again cool the gauze and add 2 more drops of Benzyl Alcohol and burn as before. This process is continued until a total of 6 drops has been added and ignited. Then hold the gauze in the outer edge of the Bunsen flame, adjusted to a height of about 4 cm.: not even a transient green color is imparted to the flame.

Aldehyde—Transfer 5.0 ml. of Benzyl Alcohol to a 250-ml. conical flask containing 75 ml. of a reagent prepared by dissolving 34.7 g. of hydroxylamine hydrochloride in 160 ml. of water and diluting this solution to 1000 ml. with alcohol. Allow to stand for 10 minutes, add 1 ml. of bromophenol blue T.S. and titrate to a light green end-point with 0.1 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations*, page 883). Match the color of the end-point with that of the titrated sample solution: the net volume of 0.1 *N* sodium hydroxide consumed does not exceed 1.0 ml. (0.2 percent as benzaldehyde).

Packaging and storage—Preserve Benzyl Alcohol in tight containers, remote from fire.

CATEGORY—Bacteriostatic (injections).

Benzyl Benzoate Lotion

Benzyl Benzoate Lotion contains not less than 26.0 percent and not more than 30.0 percent (w/w) of $C_{14}H_{12}O_2$.

Benzyl Benzoate	**250 ml.**
Triethanolamine	**5 g.**
Oleic acid	**20 g.**
Purified Water	**750 ml.**
To make about	**1000 ml.**

Mix the triethanolamine with the oleic acid, add the benzyl benzoate, and mix. Transfer the mixture to a suitable container of about 2000-ml. capacity, add 250 ml. of purified water, and shake the mixture thoroughly. Finally add the remaining 500 ml. of purified water, and again shake thoroughly.

pH, page 824—The pH of Benzyl Benzoate Lotion is between 8.5 and 9.2.

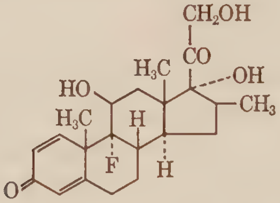
Assay—Place about 5 g. of Benzyl Benzoate Lotion, accurately weighed, in a conical flask. Add 25 ml. of alcohol and 2 drops of phenolphthalein T.S. Cool the solution to about 15°, and titrate quickly with 0.1 *N* sodium hydroxide to a slight pink color. Add 50.0 ml. of 0.5 *N* alcoholic potassium hydroxide, connect the flask to a reflux condenser, and boil gently for 1 hour. Cool, promptly add phenolphthalein T.S., and titrate with 0.5 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 0.5 *N* alcoholic potassium hydroxide is equivalent to 106.1 mg. of $C_{14}H_{12}O_2$.

Packaging and storage—Preserve Benzyl Benzoate Lotion in tight containers.

CATEGORY—Scabicide.

FOR EXTERNAL USE—Topically, as lotion over previously dampened skin of entire body, except face.

Betamethasone*



9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione

$C_{22}H_{29}FO_5$ Mol. wt. 392.47

Betamethasone contains not less than 96.0 percent and not more than 104.0 percent of $C_{22}H_{29}FO_5$, calculated on the dried basis.

Description—Betamethasone occurs as a white to practically white, odorless, crystalline powder. When tested by the method under *Class Ia,* page 815, it melts at about 240° with some decomposition.

Solubility—Betamethasone is sparingly soluble in acetone, in alcohol, in dioxane, and in methanol. It is very slightly soluble in chloroform, and in ether, and is insoluble in water.

Identification—Prepare a solution of Betamethasone in chloroform containing 500 mcg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution and 10 μl. of a chloroform solution of NF Betamethasone Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and diethylamine (2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear. The R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Betamethasone, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Betamethasone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Betamethasone in methanol exhibits maxima and minima at the same wavelengths as that of NF Betamethasone Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 239 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Betamethasone, calculated on the dried basis, determined in a solution in dioxane containing 100 mg. of Betamethasone in each 10 ml., is between +112° and +120°.

Loss on drying, page 814—Dry Betamethasone at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Betamethasone yields not more than 0.2 percent of residue on ignition.

Foreign steroids and other impurities—*Standard preparation*—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Betamethasone Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Betamethasone previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Pur-*

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* Patent pending. See notice, page ii.

ity, page 876, using a solvent system consisting of chloroform, methanol, and water (90:7.5:0.5). Use 25.0 ml. of methanol, rather than dehydrated alcohol, to elute the steroid from the silica gel. Determine the absorbance at the maximum at about 240 mμ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Betamethasone taken: not more than 3 percent is found.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay,* page 876, using NF Betamethasone Reference Standard.

Assay preparation—Weigh accurately about 100 mg. of Betamethasone, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Pipet 5.0 ml. of this solution into a 250-ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask.

Procedure—Proceed as directed under *Steroid Assay,* page 876, except add 1.0 ml. of glacial acetic acid after maintaining at 45 ± 1° for 90 minutes. Calculate the quantity, in mg., of $C_{22}H_{29}FO_5$ in the portion of Betamethasone taken by the formula $10C \times (A_U/A_S)$.

Packaging and storage—Preserve Betamethasone in well-closed containers.

CATEGORY—Glucocorticoid.

USUAL DOSE—Initial, **2.4** to **4.8 mg.** daily in divided doses; maintenance, **600 mcg.** to **1.2 mg.** daily.

USUAL DOSE RANGE—**600 mcg.** to **8.4 mg.** daily.

APPLICATION—Topically, as a 0.2 percent cream applied to the skin two or three times a day.

Betamethasone Cream

Betamethasone Cream is betamethasone in a suitable water-miscible base. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{22}H_{29}FO_5$.

Identification—Concentrate 30 ml. of the first dilution obtained in the *Assay preparation* to 3 ml. on a steam bath, and apply 10 μl. of the solution to a thin-layer chromatographic plate coated with a 0.25-mm. layer of silica gel G. Apply to the same plate 10 μl. of a solution containing 1 mg. per ml. of NF Betamethasone Reference Standard in dehydrated alcohol. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and diethylamine (2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, and allow the solvent to evaporate. Spray the plate with a mixture of sulfuric acid, methanol, and nitric acid (10:10:1), and heat at 105° for 10 minutes: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Weight variation, page 901—Betamethasone Cream meets the requirements of the weight variation test for creams.

Assay—

Standard preparation—Prepare, by quantitative and stepwise dilution, a solution in dehydrated alcohol containing about 10 mcg. per ml. of NF Betamethasone Reference Standard, previously dried at 105° for 3 hours and accurately weighed.

Assay preparation—Transfer an accurately weighed portion of Betamethasone Cream, equivalent to about 10 mg. of betamethasone, to a beaker, add 40 ml. of dehydrated alcohol, and warm on a steam bath with constant stirring for 20 minutes. Chill in an ice water bath for 30 minutes, and filter through a medium-porosity, sintered-glass funnel into a 100-ml. volumetric flask. Transfer the residue on the funnel to the beaker, add 40 ml. of dehydrated alcohol, warm and then chill as described herein, and filter through the funnel into the same volumetric flask. Allow the contents of the flask to come to room temperature, dilute to volume with dehydrated alcohol, and mix. (Retain 30 ml. of this solution for the *Identification test.*) Pipet 10.0 ml. into a second 100-ml. volumetric flask, dilute to volume with dehydrated alcohol, and mix.

Procedure—Flush three low-actinic glass-stoppered, 50-ml. conical flasks with a stream of nitrogen for 10 seconds and stopper. Pipet 20.0 ml. of the *Standard preparation* into one flask, 20.0 ml. of the *Assay preparation* into the second flask, and 20.0 ml. of dehydrated alcohol into the last flask to serve as the blank. To each flask add 2.0 ml. each of a 1 in 200 solution of triphenyltetrazolium chloride in alcohol and a 3 in 20 solution of tetramethylammonium hydroxide (1 in 10) in alcohol, mix, flush with nitrogen, and stopper. Maintain the flasks at 45° for 30 minutes in a water bath, then add 1.0 ml. of glacial acetic acid to each flask, and allow to cool to room temperature. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 485 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{29}FO_5$ in the portion of the Cream taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Betamethasone Cream in collapsible tubes, or in tight containers.

Cream available—Betamethasone Cream usually available contains 0.2 percent of betamethasone.

CATEGORY and APPLICATION—See Betamethasone.

Betamethasone Tablets

Betamethasone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{29}FO_5$.

Identification—Evaporate 50 ml. of the *Assay preparation* from the *Assay* on a steam bath just to dryness and dissolve the residue in 1 ml. of chloroform. Proceed as directed for *Identification* under *Betamethasone*, page 86, beginning with "On a suitable thin-layer chromatographic plate. . . ."

Disintegration, page 878—The disintegration time limit for Betamethasone Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Betamethasone Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay,* page 876, using NF Betamethasone Reference Standard.

Assay preparation—Weigh and finely powder not less than 10 Betamethasone Tablets. Weigh accurately a portion of the powder, equivalent to about 2.5 mg. of betamethasone, and transfer with the aid of 15 ml. of water to a separator. Extract the betamethasone completely, using four 25-ml. portions of chloroform, filtering each extract through chloroform-washed cotton into a 250-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask, evaporate the chloroform on a steam bath just to dryness, cool, and dissolve the residue in 20.0 ml. of alcohol.

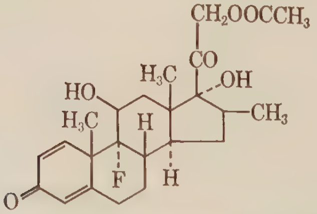
Procedure—Proceed as directed under *Steroid Assay,* page 876, except add 1.0 ml. of glacial acetic acid after maintaining at 45 ± 1° for 90 minutes. Calculate the quantity, in mg., of $C_{22}H_{29}FO_5$ in the portion of the Tablets taken by the formula $0.25\ C \times (A_U/A_S)$.

Packaging and storage—Preserve Betamethasone Tablets in well-closed containers.

Tablets available—Betamethasone Tablets usually available contain the following amount of betamethasone: 600 mcg.

CATEGORY AND DOSE—See Betamethasone.

Betamethasone Acetate*



9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 21-Acetate

$C_{24}H_{31}FO_6$ Mol. wt. 434.51

Betamethasone Acetate contains not less than 97.0 percent and not more than 103.0 percent of $C_{24}H_{31}FO_6$, calculated on the anhydrous basis.

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* Patented. See notice, page ii.

Description—Betamethasone Acetate occurs as a white to creamy white, odorless powder. When tested by the method under *Class Ia*, page 814, it sinters and resolidifies at about 165°, and remelts with decomposition between 200° and 220°.

Solubility—Betamethasone Acetate is practically insoluble in water. It is freely soluble in acetone, and is soluble in alcohol and in chloroform.

Identification—

A: Prepare a solution of Betamethasone Acetate in chloroform containing 500 mcg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a chloroform solution of NF Betamethasone Acetate Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and diethylamine (2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

B: To about 50 mg. of Betamethasone Acetate contained in a test tube, add 2 ml. of alcoholic potassium hydroxide T.S., and heat in a boiling water bath for 5 minutes. Cool, add 2 ml. of dilute sulfuric acid (1 in 3.5), and boil gently for about 1 minute: the odor of ethyl acetate is perceptible.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Betamethasone Acetate, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Betamethasone Acetate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Betamethasone Acetate in methanol exhibits maxima and minima at the same wavelengths as that of NF Betamethasone Acetate Reference Standard, similarly measured, and the respective absorptivities, at the point of maximum absorbance occurring at about 239 mµ, do not differ by more than 2.5 percent.

Specific rotation, page 822—The specific rotation of Betamethasone Acetate, calculated on the anhydrous basis, determined in a solution in dioxane containing 100 mg. of Betamethasone Acetate in each 10 ml., is between +120° and +128°.

Water, page 900—Determine the water content of Betamethasone Acetate by the titrimetric method: not more than 4 percent is found.

Residue on ignition—The residue on ignition from 100 mg. of Betamethasone Acetate is negligible.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Betamethasone Acetate Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Betamethasone Acetate previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of chloroform, methanol and water (90:7.5:0.5). Use 25.0 ml. of methanol, rather than dehydrated alcohol, to elute the steroid from the silica gel. Determine the absorbance at the maximum at about 240 mµ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Betamethasone Acetate taken: not more than 3 percent is found.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using NF Betamethasone Acetate Reference Standard, except prepare a solution in alcohol containing about 20 mcg. per ml., and pipet 20.0 ml. into a glass-stoppered, 50-ml. low-actinic flask.

Assay preparation—Dissolve about 100 mg. of Betamethasone Acetate, accurately weighed, in sufficient alcohol to make 200.0 ml., and mix. Pipet 10.0 ml. of this solution into a 250-ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered, 50-ml. low-actinic flask.

Procedure—Proceed as directed under *Steroid Assay*, page 876, except keep the flasks in a constant-temperature bath at 50° for 90 minutes, and then add 1.0 ml. of glacial acetic acid. Calculate the quantity, in mg., of $C_{24}H_{31}FO_6$ in the portion of Betamethasone Acetate taken by the formula $5C \times (A_U/A_S)$.

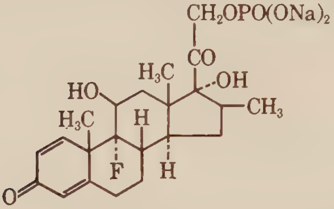
Packaging and storage—Preserve Betamethasone Acetate in tight containers.

CATEGORY—Glucocorticoid.

USUAL DOSE—See Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension.

Betamethasone Acetate and Betamethasone Sodium Phosphate Suspension, Sterile, page 91

Betamethasone Sodium Phosphate*



9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 21-(Disodium Phosphate)

$C_{22}H_{28}FNa_2O_8P$ Mol. wt. 516.42

Betamethasone Sodium Phosphate contains not less than 97.0 percent and not more than 103.0 percent of $C_{22}H_{28}FNa_2O_8P$, calculated on the anhydrous basis.

Description—Betamethasone Sodium Phosphate occurs as a white to practically white, odorless powder. It is hygroscopic.

Solubility—Betamethasone Sodium Phosphate is freely soluble in water and in methanol. It is practically insoluble in acetone and in chloroform.

Identification—

A: Prepare a solution of Betamethasone Sodium Phosphate in a benzene-alcohol-water mixture (5:5:1) containing 1 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution and 10 μl. of a benzene-alcohol-water (5:5:1) solution of NF Betamethasone Sodium Phosphate Reference Standard containing 1 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system, consisting of *n*-butyl alcohol saturated with 1 *N* hydrochloric acid, until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by spraying the plate with a mixture of sulfuric acid, methanol, and nitric acid (10:10:1), and then heating at 105° for 10 minutes: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

B: Ignite Betamethasone Sodium Phosphate at 800° (page 858): the residue responds to the tests for *Sodium*, page 810, and for *Phosphate*, page 809.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Betamethasone Sodium Phosphate, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Betamethasone Sodium Phosphate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Betamethasone Sodium Phosphate in water exhibits maxima and minima at the same wavelengths as that of NF Betamethasone Sodium Phosphate Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Betamethasone Sodium Phosphate, calculated on the anhydrous basis, determined in a solution in water containing 100 mg. of Betamethasone Sodium Phosphate in each 10 ml., is between +99° and +105°.

Water, page 900—Determine the water content of Betamethasone Sodium Phosphate by the titrimetric method: not more than 10 percent is found.

Phosphate ions—

Ammonium molybdate solution—Dissolve 6.4 g. of ammonium molybdate in 40 ml. of water. Add 50 ml. of 10 *N* sulfuric acid, shake, and dilute to 100.0 ml. with water. This solution is stable for approximately 2 weeks.

Stannous chloride solution—Dissolve 1.0 g. of stannous chloride in 5.0 ml. of hydrochloric acid. Dilute 1.0 ml. of this solution to 100 ml. with water just before use.

Procedure—Dissolve about 200 mg. of Betamethasone Sodium Phosphate, accurately weighed, in sufficient water to make 100.0 ml., and mix. Pipet 10.0 ml. of this solution in a 100-ml. volumetric flask containing 50 ml. of water, add 10.0 ml. of 10 *N* sulfuric acid, 10.0 ml. of *Ammonium*

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* Patented. See notice, page ii.

molybdate solution, and 10.0 ml. of water, mixing well after each addition. Slowly, with shaking, add 5.0 ml. of *Stannous chloride solution*, dilute to volume with water, stopper, mix, and allow to stand for 10 minutes. Determine the absorbance of the solution at 675 mμ, with a suitable spectrophotometer: the absorbance does not exceed that of 10 ml. of a solution of sodium phosphate prepared in water to contain 20 mcg. of phosphate (PO_4) in each ml. and treated as directed above, beginning with "Pipet 10.0 ml. of this solution . . ." (1 percent).

Free betamethasone—Dissolve about 25.0 mg. of Betamethasone Sodium Phosphate, accurately weighed, in sufficient water to make 25.0 ml. Pipet 5.0 ml. of the solution into a separator, and extract with three 25-ml. portions of chloroform. Filter each extract through a chloroform-saturated cotton pledget, combining the filtrates in a conical flask. Evaporate the chloroform to dryness on a steam bath with the aid of a current of air, and dissolve the residue in 25.0 ml. of methanol. Determine the absorbance (A) of this solution at the maximum at about 240 mμ, in a 1-cm. cell, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of free betamethasone in the sample of Betamethasone Sodium Phosphate taken by the formula $3.125 \times A$: not more than 250 mcg. is found (1 percent).

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Betamethasone Sodium Phosphate Reference Standard and a 1:2 mixture of water and acetone as the solvent.

Test preparation—Weigh accurately about 80 mg. of Betamethasone Sodium Phosphate, previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a 1:2 mixture of water and acetone to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of *n*-butanol saturated with 1 *N* hydrochloric acid. Use 25.0 ml. of water, rather than dehydrated alcohol, to elute the steroid from the silica gel. Determine the absorbance at the maximum at about 242 mμ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Betamethasone Sodium Phosphate taken: not more than 3 percent is found.

Assay—Weigh accurately about 50 mg. of Betamethasone Sodium Phosphate, dissolve in sufficient water to make 250.0 ml., and mix. Dilute 10.0 ml. of this solution to 100.0 ml. of water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Betamethasone Sodium Phosphate Reference Standard, in the same medium, at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{22}H_{28}FNa_2O_8P$ in the portion of Betamethasone Sodium Phosphate taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Betamethasone Sodium Phosphate in tight containers.

CATEGORY—Glucocorticoid.

USUAL DOSE—See Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension.

Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension

Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension is a sterile preparation of betamethasone sodium phosphate in solution and betamethasone acetate in suspension in water for injection. It contains an amount of $C_{22}H_{28}FNa_2O_8P$ (betamethasone sodium phosphate) equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{22}H_{29}FO_5$ (betamethasone), and not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{31}FO_6$ (betamethasone acetate).

Identification—

A: Dilute 2 ml. of Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension with 2 ml. of methanol. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a methanol-water solution (1:1) of NF Betamethasone Sodium Phosphate Reference Standard containing 2 mg. per ml. Proceed as directed for *Identification test A* under *Betamethasone Sodium Phosphate*, page 90, beginning with "Allow the spots to dry. . . ."

B: On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of the solution prepared for *Identification test A* and 10 µl. of a methanol-water solution (1:1) of NF Betamethasone Acetate Reference Standard containing 1.5 mg. per ml. Proceed as directed for *Identification test A* under *Betamethasone Acetate*, page 88, beginning with "Allow the spots to dry. . . ."

pH, page 824—The pH of Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension is between 6.8 and 7.2.

Other requirements—Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension meets the requirements under *Injections*, page 810.

Assay for betamethasone sodium phosphate—

Standard preparation—Weigh accurately about 40 mg. of NF Betamethasone Sodium Phosphate Reference Standard, dissolve in sufficient 0.1 *N* hydrochloric acid to make 250.0 ml., and mix.

Assay preparation—Pipet, with a "to contain" pipet, a volume of Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension, equivalent in betamethasone sodium phosphate content to 6 mg. of betamethasone, into a 50-ml. volumetric flask, rinse the pipet with 0.1 *N* hydrochloric acid adding the rinsings to the flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix.

Procedure—Transfer 40.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate separators. Extract each preparation with three 40-ml. portions of chloroform, and wash the aqueous phase with 40 ml. of solvent hexane. Pipet 20.0 ml. of the aqueous phase into a 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 241 mµ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{29}FO_5$ (betamethasone), equivalent to the quantity of $C_{22}H_{28}FNa_2O_8P$ (betamethasone sodium phosphate), in each ml. of the Suspension taken by the formula $0.05 \times (C/V) \times 0.7585 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., calculated on the anhydrous basis, of NF Betamethasone Sodium Phosphate Reference Standard in the *Standard preparation*, V is the volume, in ml., of the Suspension taken, and 0.7585 is the factor converting betamethasone sodium phosphate to betamethasone.

Assay for betamethasone acetate—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using NF Betamethasone Acetate Reference Standard, except prepare a solution in alcohol containing about 22.5 mcg. per ml.

Assay preparation—Pipet, with a "to contain" pipet, a volume of Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension, equivalent to about 15 mg. of betamethasone acetate, into a fine-porosity, sintered-glass funnel, and rinse the pipet with 1 ml. of cold water, adding the rinsings to the funnel. Wash the residue on the funnel with 1 ml. of cold water, and discard the filtrate. Dissolve the residue in 25 ml. of alcohol, wash the funnel with two 4-ml. portions of alcohol, transfer the alcohol solutions to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Pipet 15.0 ml. of this solution into a 100-ml. volumetric flask, dilute to volume with alcohol, and mix.

Procedure—Transfer 20.0 ml. each of the *Standard preparation* and of the *Assay preparation*, to separate low-actinic 50-ml. flasks, and proceed as directed under *Steroid Assay*, page 876, but keep the flasks in a constant-temperature bath at 50° for 90 minutes, and then add 1.0 ml. of glacial acetic acid. Calculate the quantity, in mg., of $C_{24}H_{31}FO_6$ in each ml. of the Suspension taken by the formula $0.667 \times (C/V) \times (A_U/A_S)$.

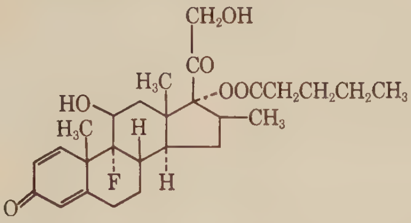
Packaging and storage—Preserve Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension in multiple-dose containers, preferably of Type I glass.

Suspension available—Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension usually available contains the following amounts of betamethasone sodium phosphate and betamethasone acetate: betamethasone sodium phosphate, equivalent to 15 mg. of betamethasone, and 15 mg. of betamethasone acetate in 5 ml.

CATEGORY—Glucocorticoid.

USUAL DOSE—Intramuscular, **1 ml.** (equivalent to 3 mg. of betamethasone acetate and 3 mg. of betamethasone) repeated at intervals of 3 days to 1 week. Intra-articular, **0.25** to **2 ml.** depending on the size of the joint.

Betamethasone Valerate*



9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-Valerate

$C_{27}H_{37}FO_6$ Mol. wt. 476.59

Betamethasone Valerate contains not less than 97.0 percent and not more than 103.0 percent of $C_{27}H_{37}FO_6$, calculated on the dried basis.

Description—Betamethasone Valerate occurs as a white to practically white, odorless powder. When tested by the method under *Class Ia*, page 815, it melts at about 190° with decomposition.

Solubility—Betamethasone Valerate is freely soluble in acetone and in chloroform. It is soluble in alcohol, slightly soluble in benzene and in ether, and is practically insoluble in water.

Identification—Prepare a solution of Betamethasone Valerate in chloroform–methylene chloride (1:1) containing 500 mcg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 10 µl. of this solution and 10 µl. of a solution of NF Betamethasone Valerate Reference Standard in chloroform–methylene chloride (1:1) containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of benzene and ethyl acetate (1:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, and allow the solvent to evaporate. Spray the plate with a mixture of sulfuric acid, methanol, and nitric acid (10:10:1), and heat at 105° for 15 minutes: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Betamethasone Valerate, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Betamethasone Valerate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Betamethasone Valerate in methanol exhibits maxima and minima at the same wavelengths as that of NF Betamethasone Valerate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 239 mµ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Betamethasone Valerate, previously dried at 105° for 3 hours, determined in a solution in dioxane containing 100 mg. of Betamethasone Valerate in each 10 ml., is between +75° and +82°.

Loss on drying, page 814—Dry Betamethasone Valerate at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Betamethasone Valerate yields not more than 0.1 percent of residue on ignition.

Foreign steroids and other impurities—*Standard preparation*—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Betamethasone Valerate Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Betamethasone Valerate previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and ethyl acetate (1:1). Use 25.0 ml. of methanol, rather than dehydrated alcohol, to elute the steroid from the silica gel. Determine the absorbance at the maximum at about 239 mµ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Betamethasone Valerate taken: not more than 3 percent is found.

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* Patented. See notice, page ii.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay,* page 876, using NF Betamethasone Valerate Reference Standard, except prepare a solution in alcohol containing about 20 mcg. per ml., and pipet 20.0 ml. into a glass-stoppered, low-actinic 50-ml. flask.

Assay preparation—Weigh accurately about 50 mg. of Betamethasone Valerate, dissolve it in sufficient alcohol to make 100.0 ml., and mix. Pipet 4.0 ml. of this solution into a 100-ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered, low-actinic 50-ml. flask.

Procedure—Proceed as directed under *Steroid Assay,* page 876, except keep the flasks in a constant-temperature bath at 45° for 90 minutes, and then add 1.0 ml. of glacial acetic acid. Calculate the quantity, in mg., of $C_{27}H_{37}FO_6$ in the portion of Betamethasone Valerate taken by the formula $2.5C \times (A_U/A_S)$.

Packaging and storage—Preserve Betamethasone Valerate in tight containers.

Category—Glucocorticoid.

Application—Topically as a cream, containing the equivalent of 0.1 percent of betamethasone, to the affected area one to three times a day.

Betamethasone Valerate Cream

Betamethasone Valerate Cream contains an amount of $C_{27}H_{37}FO_6$ (betamethasone valerate), equivalent to not less than 95.0 percent and not more than 115.0 percent of the labeled amount of $C_{22}H_{29}FO_5$ (betamethasone), in a suitable cream base.

Identification—Evaporate to dryness on a steam bath the remaining alcoholic filtrate, obtained as directed in the *Assay* under *Assay preparation,* and dissolve the residue in 3 ml. of chloroform–methylene chloride (1:1). This solution responds to the *Identification test* under *Betamethasone Valerate,* page 93.

Weight variation, page 901—Betamethasone Valerate Cream meets the requirements of the weight variation test for creams.

Assay—

Equilibrated chloroform—Equilibrate 50-ml. portions of chloroform with a mixture of 20 ml. of water and 2 ml. of 0.1 *N* hydrochloric acid. Use a new water-acid mixture for each 200 ml. of chloroform, equilibrating about 700 ml. for each assay to be performed.

Standard preparation—Transfer about 30 mg. of NF Betamethasone Valerate Reference Standard, accurately weighed, to a 50-ml. volumetric flask, dissolve in and dilute to volume with *Equilibrated chloroform,* and mix. Pipet 4.0 ml. of this solution into a 200-ml. volumetric flask, add *Equilibrated chloroform* to volume, and mix.

Assay preparation—Transfer an accurately weighed amount of Betamethasone Valerate Cream, equivalent to about 2 mg. of betamethasone, to a separator, add 20 ml. of water and 2 ml. of 0.1 *N* hydrochloric acid, and mix. Extract with four 50-ml. portions of chloroform, and combine the extracts.

Procedure—Filter the *Standard preparation,* the *Assay preparation,* and 200 ml. of *Equilibrated chloroform* to serve as the blank through cotton pledgets, previously layered over with anhydrous sodium sulfate and washed with a few ml. of chloroform, into separate beakers. Wash the funnels with three 5-ml. portions of chloroform, add the washes to the beakers, and evaporate the filtrates to dryness on a steam bath under a current of dry nitrogen. Add 25 ml. of alcohol to the residues, heat on a steam bath for 5 minutes, stirring occasionally, and then cool the solutions to room temperature. Transfer the solutions to separate 100-ml. volumetric flasks (a waxy white mass may settle out on cooling and addition of alcohol; do not transfer this substance to the volumetric flasks), dilute to volume with alcohol, and mix. Filter the solutions through paper, discarding the first 10 ml. of filtrate. Pipet 20.0 ml. of each filtrate into separate low-actinic, glass-stoppered 50-ml. flasks, pipet 2.0 ml. of blue tetrazolium T.S. into each flask, mix, then add 2.0 ml. of dilute tetramethylammonium hydroxide T.S. in alcohol (1 in 10) to each flask. Mix, maintain in a constant-temperature bath at 45° for 90 minutes, remove from the bath, and immediately add 1.0 ml. of glacial acetic acid. Swirl the contents of the flasks, cool in an ice-water bath for 1 minute, and then allow the contents to come to room temperature. Concomitantly determine the absorbance of the solutions in 1-cm. cells, at the maximum at about 525 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{29}FO_5$ (betamethasone) equivalent to the quantity of $C_{27}H_{37}FO_6$ (betamethasone valerate) in the portion of the Cream taken by the formula $0.2C \times 0.8235 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Betamethasone

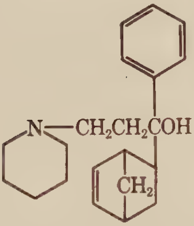
Valerate Reference Standard in the *Standard preparation*, and 0.8235 is the factor converting betamethasone valerate to betamethasone.

Packaging and storage—Preserve Betamethasone Valerate Cream in collapsible tubes, or in tight containers.

Cream available—Betamethasone Valerate Cream usually available contains betamethasone valerate equivalent to 0.1 percent of betamethasone.

CATEGORY and APPLICATION—See Betamethasone Valerate.

Biperiden*



α-5-Norbornen-2-yl-α-phenyl-1-piperidinepropanol

$C_{21}H_{29}NO$ Mol. wt. 311.47

Biperiden contains not less than 98.0 percent and not more than 101.0 percent of $C_{21}H_{29}NO$, calculated on the dried basis.

Description—Biperiden occurs as a white, practically odorless, crystalline powder.

Solubility—Biperiden is practically insoluble in water. It is sparingly soluble in ethanol and freely soluble in chloroform.

Identification—

A: Dissolve about 20 mg. of Biperiden in 5 ml. of 85 percent phosphorus acid: a green color is produced.

B: Dissolve 200 mg. of Biperiden in 80 ml. of water with the aid of 0.5 ml. of 25 percent hydrochloric acid, warming if necessary to effect solution, and then cool. To 5 ml. of the solution add 1 drop of hydrochloric acid and several drops of mercuric chloride T.S.: a white precipitate is formed. To a second 5-ml. portion of the solution add bromine T.S. dropwise: a yellow precipitate forms which redissolves on shaking, and finally, upon the addition of more bromine T.S., a permanent precipitate forms.

Melting range, page 814—Biperiden melts between 112° and 116°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Biperiden, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Biperiden Reference Standard, similarly measured.

Ultraviolet absorption, page 866—Transfer about 180 mg. of Biperiden, accurately weighed, to a 200-ml. volumetric flask, add 1 ml. of lactic acid, dilute to volume with water, and mix. The ultraviolet absorption spectrum of this solution exhibits maxima and minima at the same wavelengths as that of NF Biperiden Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 257 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Biperiden at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Biperiden yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 500 mg. of Biperiden, accurately weighed, in 20 ml. of benzene, add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to an emerald-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 31.15 mg. of $C_{21}H_{29}NO$.

Packaging and storage—Preserve Biperiden in well-closed, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE—Intramuscular, **2 mg.** (as the lactate) which may be repeated every half-hour until relief is obtained, but no more than four consecutive doses should be given in a 24-hour period; intravenous, **5 mg.** (as the lactate) given slowly, this dose may be repeated once in a 24-hour period.

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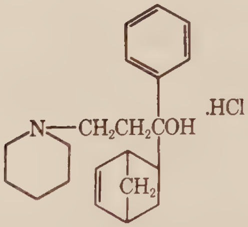
* Patented. See notice, page ii.

Biperiden Hydrochloride*



α-5-Norbornen-2-yl-α-phenyl-1-piperidinepropanol Hydrochloride

$C_{21}H_{29}NO.HCl$ Mol. wt. 347.93

Biperiden Hydrochloride contains not less than 98.0 percent and not more than 101.0 percent of $C_{21}H_{29}NO.HCl$, calculated on the dried basis.

Description—Biperiden Hydrochloride occurs as a white, practically odorless, crystalline powder. It melts at about 275° with decomposition. It is optically inactive.

Solubility—Biperiden Hydrochloride is slightly soluble in water and in ether, sparingly soluble in methanol, and slightly soluble in alcohol and in chloroform.

Identification—

A: Dissolve about 20 mg. of Biperiden Hydrochloride in 5 ml. of 85 percent phosphoric acid: a green color is produced.

B: To 5 ml. of a solution of Biperiden Hydrochloride (1 in 500) add bromine T.S. dropwise: a yellow precipitate, which dissolves on shaking, is formed. Addition of more bromine T.S. produces a precipitate which does not dissolve on shaking.

C: A 5-ml. portion of a solution of Biperiden Hydrochloride (1 in 500) responds to the tests for *Chloride*, page 808.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Biperiden Hydrochloride, previously dried at 105° for 3 hours, exhibits maxima and minima at the same wavelengths as that of NF Biperiden Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 1000 solution of Biperiden Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Biperiden Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 257 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Biperiden Hydrochloride at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Assay—Weigh accurately about 500 mg. of Biperiden Hydrochloride, and dissolve in 80 ml. of glacial acetic acid, warming slightly if necessary to effect solution. Cool, add 1 drop of crystal violet T.S. and 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to an emerald-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 34.79 mg. of $C_{21}H_{29}NO.HCl$.

Packaging and storage—Preserve Biperiden Hydrochloride in well-closed, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE RANGE—**2 mg.** three to four times a day.

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* Patented. See notice, page ii.

Biperiden Hydrochloride Tablets

Biperiden Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{21}H_{29}NO.HCl$.

Identification—Biperiden Hydrochloride Tablets meet the requirements under *Identification—Organic Nitrogenous Bases,* page 810.

Disintegration, page 878—The disintegration time limit for Biperiden Hydrochloride Tablets is 15 minutes.

Content uniformity, *Method I,* page 799

—Biperiden Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Phosphate buffer-bromocresol purple solution—Dissolve 38 g. of monobasic sodium phosphate and 2 g. of anhydrous dibasic sodium phosphate in water to make 1000 ml. Adjust the pH of the solution to 5.3 ± 0.1, if necessary (*Solution A*). Dissolve 400 mg. of bromocresol purple in 30 ml. of water, add 6.3 ml. of 0.1 *N* sodium hydroxide, and dilute to 500 ml. with water (*Solution B*). Mix equal volumes of *Solution A*, *Solution B*, and chloroform, shake for about 5 minutes in a separator, and discard the chloroform.

Standard preparation—Transfer about 80 mg. of NF Biperiden Hydrochloride Reference Standard, previously dried at 105° for 3 hours and accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 5.0 ml. of this solution to a second 100-ml. volumetric flask, add 25 ml. of water, dilute to volume with methanol, and mix.

Assay preparation—Weigh and finely powder not less than 20 Biperiden Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 2 mg. of biperiden hydrochloride, to a 50-ml. volumetric flask, add 12.5 ml. of water, and heat on a steam bath for 15 minutes. Cool, dilute to volume with methanol, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of a methanol-water mixture (3:1) to separate separators each containing 10.0 ml. of *Phosphate buffer-bromocresol purple solution*. Extract the solution in each separator for 10 minutes with 40.0 ml. of chloroform. After the layers have separated, filter each chloroform extract through Whatman No. 31 or equivalent filter paper into separate glass-stoppered containers, discarding the first 10 ml. of filtrate. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 408 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{29}NO.HCl$ in the portion of Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Biperiden Hydrochloride Tablets in tight containers.

Tablets available—Biperiden Hydrochloride Tablets usually available contain the following amount of biperiden hydrochloride: 2 mg.

CATEGORY and DOSE—See Biperiden Hydrochloride.

Biperiden Lactate Injection

Biperiden Lactate Injection is a sterile solution of $C_{21}H_{29}NO.C_3H_6O_3$ (biperiden lactate) in water for injection, prepared from biperiden with the aid of lactic acid. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{21}H_{29}NO.C_3H_6O_3$.

Identification—The ultraviolet absorption spectrum of Biperiden Lactate Injection, diluted with water to a concentration of about 1 mg. of biperiden lactate per ml., exhibits maxima and minima at the same wavelengths as that of a similar solution of NF Biperiden Reference Standard prepared with the aid of lactic acid solution (1 in 200) and similarly measured.

pH, page 824—The pH of Biperiden Lactate Injection is between 4.8 and 5.8.

Other requirements—Biperiden Lactate Injection meets the requirements under *Injections*, page 810.

Assay—

Phosphate buffer-bromocresol purple solution—Dissolve 38 g. of monobasic sodium phosphate and 2 g. of anhydrous dibasic sodium phosphate in water to make 1000 ml. Adjust the pH of the solution to 5.3 ± 0.1, if necessary (*Solution A*). Dissolve 400 mg. of bromocresol purple in 30 ml. of water, add 6.3 ml. of 0.1 *N* sodium hydroxide, and dilute to 500 ml. with water (*Solution B*). Mix equal volumes of *Solution A*, *Solution B*, and chloroform, shake for about 5 minutes in a separator, and discard the chloroform.

Standard preparation—Transfer about 80 mg. of NF Biperiden Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 5.0 ml. of this solution to a second 100-ml. volumetric flask, add 25 ml. of water, dilute to volume with methanol, and mix.

Assay preparation—Transfer an accurately measured volume of Biperiden Lactate Injection, equivalent to about 5 mg. of biperiden lactate, to a 100-ml. volumetric flask, add 25 ml. of water, dilute to volume with methanol, and mix.

Procedure—Transfer 5.0 ml. each of the

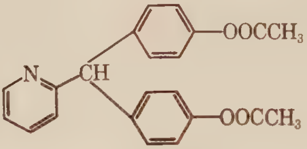
Standard preparation, of the *Assay preparation*, and of a methanol-water mixture (3:1) to serve as the blank to separate separators, each containing 10.0 ml. of *Phosphate buffer-bromocresol purple solution.* Extract the solution in each separator for 10 minutes with 50.0 ml. of chloroform. After the layers have separated, filter each chloroform extract through Whatman No. 31 or equivalent filter paper into separate glass-stoppered containers, discarding the first 10 ml. of filtrate. Concomitantly determine the absorbance of the subsequent filtrate from each solution in 1-cm. cells, at the maximum at about 408 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S, and that from the *Assay preparation* as A_U. Calculate the quantity, in mg. of $C_{21}H_{29}NO.C_3H_6O_3$ in each ml. of the Injection taken by the formula $0.1 \times (C/V) \times 1.289 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, V is the volume, in ml., of the Injection taken, and 1.289 is the factor converting biperiden to biperiden lactate.

Packaging and storage—Preserve Biperiden Lactate Injection in single-dose containers, preferably of Type I glass, protected from light.

Injection available—Biperiden Lactate Injection usually available contains the following amount of biperiden lactate: 5 mg. in 1 ml.

CATEGORY and DOSE—See Biperiden.

Bisacodyl*



4,4′-(2-Pyridylmethylene)diphenol Diacetate (ester)

$C_{22}H_{19}NO_4$ Mol. wt. 361.40

Bisacodyl contains not less than 98.0 percent and not more than 101.0 percent of $C_{22}H_{19}NO_4$, calculated on the dried basis.

Caution: Avoid inhalation and contact with the eyes, skin, and mucous membranes.

Description—Bisacodyl occurs as a white to off-white, crystalline powder in which particles of the order of 50 μ in diameter or less predominate.

Solubility—Bisacodyl is very slightly soluble in water. It is freely soluble in chloroform and in alcohol, soluble in methanol and in benzene, and slightly soluble in ether.

Identification—

A: Mix about 5 mg. of Bisacodyl with 2 ml. of sulfuric acid: a cherry-red to violet color is produced.

B: Mix about 20 mg. of Bisacodyl with 1 ml. of dilute hydrochloric acid (1 in 2), and add 2 ml. of phosphomolybdic acid solution (1 in 10): a yellow precipitate, which turns blue upon the addition of 1 ml. of sodium hydroxide solution (15 in 100), is formed.

Melting range, *Class Ia*, page 815—Bisacodyl melts between 131° and 135°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Bisacodyl, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Bisacodyl Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Bisacodyl in 0.05 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Bisacodyl Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 263 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Bisacodyl at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Bisacodyl yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Bisacodyl is 10 parts per million.

Assay—Dissolve about 250 mg. of Bisacodyl, accurately weighed, in 70 ml. of glacial acetic acid, add 3 drops of *p*-

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* Patented. See notice, page ii.

naphtholbenzein T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 36.14 mg. of $C_{22}H_{19}NO_4$.

Packaging and storage—Preserve Bisacodyl in well-closed containers.

CATEGORY—Cathartic.
USUAL DOSE—Oral and rectal, **10 mg.**
USUAL DOSE RANGE—Oral, **10** to **30 mg.**

Bisacodyl Suppositories*

Bisacodyl Suppositories contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{22}H_{19}NO_4$.

Identification—Transfer a quantity of Bisacodyl Suppositories, equivalent to about 150 mg. of bisacodyl, to a 500-ml. conical flask, add 150 ml. of solvent hexane, and heat on a steam bath until the suppositories melt. Filter the solution, with the aid of vacuum, through a medium-porosity sintered-glass funnel, and wash the residue with warm solvent hexane, using about 100 ml., until free from fat. Continue the vacuum until the residue appears dry. Dissolve the residue by rinsing the filter with about 50 ml. of warm acetone, collecting the filtrate in a 150-ml. beaker, and then evaporate the filtrate on a steam bath to a volume of about 5 ml. To the residual liquid add about 75 ml. of water, heat on a steam bath for 15 minutes, and then cool. Scratch the sides of the beaker to induce crystallization, filter off the crystals, and dry at 100° for about 15 minutes: the bisacodyl so obtained melts between 129° and 135° (*Class Ia*, page 815), and responds to *Identification test A* under *Bisacodyl*, page 98.

Assay—

Standard preparation—Transfer about 50 mg. of NF Bisacodyl Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add 1 *N* hydrochloric acid to volume, and mix. Transfer 20.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with 1 *N* hydrochloric acid, and mix. Transfer 10.0 ml. of the last solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Place a number of Bisacodyl Suppositories, equivalent to about 50 mg. of bisacodyl, in a 250-ml. beaker, add 40 ml. of anhydrous ether, and warm gently on a steam bath until the suppositories melt completely. While still warm, filter the solution through a high-porosity sintered-glass funnel. Rinse the beaker and filter with two 10-ml. portions and one 5-ml. portion of hot ether. Transfer the filtrate with the aid of 25 ml. of ether to a 125-ml. separator, and extract with three 25-ml. portions of 1 *N* hydrochloric acid. Combine the hydrochloric acid extracts in a 100-ml. volumetric flask, dilute to volume with 1 *N* hydrochloric acid, and mix. Transfer 20.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with 1 *N* hydrochloric acid, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 263 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{19}NO_4$ in the Suppositories taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Bisacodyl Suppositories in tight containers at temperatures below 37°.

Suppositories available—Bisacodyl Suppositories usually available contain the following amount of bisacodyl: 10 mg.

CATEGORY and DOSE—See Bisacodyl.

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* Patented. See notice, page ii.

Bisacodyl Tablets*

Bisacodyl Tablets contain not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{22}H_{19}NO_4$. Bisacodyl Tablets are enteric-coated.

Identification—Macerate a portion of powdered Bisacodyl Tablets, equivalent to about 150 mg. of bisacodyl, with 30 ml. of chloroform, reflux on a water bath for about 10 minutes, and cool. Filter the extract, evaporate to dryness, and moisten about 5 mg. of the bisacodyl so obtained with several drops of sulfuric acid: a cherry-red to violet color is produced.

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* Patented. See notice, page ii.

Disintegration, page 878—Test Bisacodyl Tablets as directed for *Enteric-Coated Tablets*, page 879, but do not use disks. Bisacodyl Tablets do not dissolve after 1 hour of agitation in simulated gastric fluid T.S., but then dissolve within 45 minutes in simulated intestinal fluid T.S. (without disks).

Content uniformity, *Method I*, page 799—Bisacodyl Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Bisacodyl Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 25 mg. of bisacodyl, to a 50-ml. conical flask, add 20 ml. of chloroform, and shake mechanically for 15 minutes. Filter the mixture through a fine-porosity sintered-glass funnel into a 250-ml. separator, rinsing the flask and funnel with three 5-ml. portions of chloroform and collecting the rinsings in the separator. To the separator add 75 ml. of ether, and then extract with three 75-ml. portions of 1 *N* hydrochloric acid. Collect the extracts in a 250-ml. volumetric flask, dilute to volume with 1 *N* hydrochloric acid, and mix. Transfer 20.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Bisacodyl Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 263 mμ, with a suitable spectrophotometer, using 1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{22}H_{19}NO_4$ in the portion of Tablets taken by the formula $1.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Store Bisacodyl Tablets in tight containers at a temperature not exceeding 30°.

Labeling—Label Bisacodyl Tablets to indicate that they are enteric-coated.

Tablets available—Bisacodyl Tablets usually available contain the following amount of bisacodyl: 5 mg.

CATEGORY and DOSE—See Bisacodyl.

Bishydroxycoumarin Capsules

Bishydroxycoumarin Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{19}H_{12}O_6$.

Identification—

A: Fuse a portion of the contents of Bishydroxycoumarin Capsules with an equal quantity of potassium hydroxide, cool, extract the melt with 5 ml. of water, filter, and acidify the filtrate with hydrochloric acid: a white, crystalline precipitate of salicylic acid is obtained.

B: The solution prepared for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of USP Bishydroxycoumarin Reference Standard, similarly measured.

Content uniformity, *Method II*, page 798—Bishydroxycoumarin Capsules meet the requirements of the content uniformity test for capsules using the following special procedure: Quantitatively transfer the contents of one capsule to a 100-ml. volumetric flask, rinse the capsule with chloroform, and add the rinsings to the flask. Add 50 ml. of chloroform, shake mechanically for 15 minutes, dilute to volume with chloroform, and filter, discarding the first 20 ml. of filtrate. Quantitatively dilute a portion of the subsequent filtrate to provide a solution containing approximately 5 mcg. per ml. of bishydroxycoumarin. Concomitantly determine the absorbance of this solution and of a solution of USP Bishydroxycoumarin Reference Standard, previously dried at 105° for 3 hours, in the same medium at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 309 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{19}H_{12}O_6$ in the capsule by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of bishydroxycoumarin in the capsule; D is the exact concentration, in mcg. per ml., of bishydroxycoumarin in the sample solution, based upon the labeled quantity per capsule and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Transfer as completely as possible the contents of not less than 20 Bishydroxycoumarin Capsules to a tared weighing bottle, and weigh. Transfer an accurately weighed quantity of the powder, equivalent to about 50 mg. of bishydroxycoumarin, to a 100-ml. volumetric flask, add about 60 ml. of chloroform, and heat on a steam bath to boiling. Cool to room temperature, add chloroform to volume, and mix. Centrifuge about 40 ml. of this solution. Pipet 10.0 ml. of the clear solution into a 125-ml. separator, and extract with four 25-ml. portions of sodium hydroxide T.S. Combine the alkaline extracts in a 250-ml. separator, acidify with hydrochloric acid, and extract with four 25-ml. portions of chloroform. Wash the combined extracts with 25 ml. of dilute hydrochloric acid (1 in 100), and filter the chloroform solution through chloroform-washed cotton into a 200-ml. volumetric flask. Extract the acid wash with 25 ml. of chloroform, and filter the chloroform layer into the same volumetric flask. Rinse the filter with chloroform, add chloroform to volume, and mix. Pipet 20.0 ml. of this solution into a 50-ml. volumetric flask, add chloroform to volume, and mix. Concomitantly determine the absorbance of this solution and of a similarly prepared solution of USP Bishydroxycoumarin Reference Standard, previously dried at 105° for 3 hours, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 309 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{19}H_{12}O_6$ in the portion of the Capsules taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Bishydroxycoumarin Capsules in well-closed containers.

Capsules available—Bishydroxycoumarin Capsules usually available contain the following amounts of bishydroxycoumarin: 25, 50, and 100 mg.

Category—Anticoagulant.

Usual dose of bishydroxycoumarin—Initial, **200** to **300** **mg.** Maintenance, **25** to **200** **mg.** daily, according to prothrombin determinations.

Milk of Bismuth

Milk of Bismuth contains bismuth hydroxide and bismuth subcarbonate in suspension in water, and yields not less than 5.2 percent and not more than 5.8 percent (w/w) of Bi_2O_3 (bismuth trioxide).

Bismuth Subnitrate	**80 g.**
Nitric Acid	**120 ml.**
Ammonium Carbonate	**10 g.**
Strong Ammonia Solution,	
Purified Water, each, a sufficient quantity,	
To make	**1000 ml.**

Mix the bismuth subnitrate with 60 ml. of purified water and 60 ml. of nitric acid in a suitable container, and agitate, warming gently until solution is effected. Pour this solution, with constant stirring, into 5000 ml. of purified water containing 60 ml. of nitric acid. Dilute 160 ml. of strong ammonia solution with 4300 ml. of purified water in a glazed or glass vessel of at least 12,000-ml. capacity. Dissolve the ammonium carbonate in this solution, and then pour the bismuth solution quickly into it with constant stirring. If the mixture is not distinctly alkaline, add sufficient diluted ammonia solution to make it so, and allow it to stand until the precipitate has settled; then pour or siphon off the supernatant liquid, and wash the precipitate twice with purified water, by decantation. Afterward transfer the magma to a strainer of close texture, so as to provide continuous washing with purified water, the outlet tube being elevated to prevent the surface of the magma from becoming dry, and allow the operation to proceed until the washings cease to yield a pink color with phenolphthalein T.S. Then drain the moist preparation, transfer it to a graduated vessel, add sufficient purified water to make the product measure 1000 ml., and mix it thoroughly.

Note: The method of preparation as given above may be varied provided the product meets the requirements given below.

Description—Milk of Bismuth is a thick, white, opaque suspension which separates upon standing. It is odorless and almost tasteless. Milk of Bismuth is miscible with water and with alcohol.

Identification—

A: Milk of Bismuth responds to the tests for *Bismuth*, page 808, and for *Carbonate*, page 808.

B: One ml. of diluted hydrochloric acid added to 1 ml. of Milk of Bismuth produces a clear solution. Pour the clear solution into 10 volumes of water: a white precipitate is formed.

Water-soluble substances—Boil 10 ml. of Milk of Bismuth with 90 ml. of water for 10 minutes, cool, add sufficient water to make the total volume 100 ml., mix, and filter. Evaporate 50 ml. of the filtrate to dryness, and ignite it gently: the weight of the residue does not exceed 5 mg. (0.1 percent).

Alkalies and alkaline earths—Dissolve 2 ml. of Milk of Bismuth in 5 ml. of hydrochloric acid, dilute with water to 100 ml., pass in hydrogen sulfide to precipitate the bismuth completely, and filter. To 50 ml. of the clear filtrate add 5 drops of sulfuric acid, evaporate to dryness and ignite: the weight of the residue does not exceed 3 mg. (0.3 percent).

Arsenic—Evaporate 12.5 ml. of Milk of Bismuth to dryness on a steam bath, add 2 ml. of sulfuric acid, and heat until fumes of sulfur trioxide are copiously evolved. Allow to cool and then cautiously dilute with water to 35 ml. The solution meets the requirements of the *Arsenic Test*, page 777 (0.8 part per million As).

Lead—To 5 ml. of Milk of Bismuth add warm nitric acid, dropwise, until it is just dissolved, and pour the solution into 50 ml. of water: a white precipitate may form. Filter, if necessary, evaporate the filtrate on a steam bath to 15 ml., again filter, and to 10 ml. of the filtrate add an equal volume of diluted sulfuric acid: no precipitate is formed.

Assay—Evaporate to dryness an accurately weighed quantity of Milk of Bismuth and ignite the residue to constant weight. From the weight of the Bi_2O_3 so obtained determine the percentage in the sample.

Packaging and storage—Preserve Milk of Bismuth in tight containers and protect it from freezing.

Category—Astringent; antacid.

Usual dose—**5 ml.**

Bismuth Subnitrate

Bismuth Subnitrate is a basic salt which, dried at 105° for 2 hours, yields upon ignition not less than 79.0 percent of Bi_2O_3 (bismuth trioxide).

Description—Bismuth Subnitrate occurs as a white, slightly hygroscopic powder. When brought in contact with moistened blue litmus paper, it shows an acid reaction.

Solubility—Bismuth Subnitrate is practically insoluble in water and in alcohol, but is readily dissolved by hydrochloric or nitric acid.

Identification—Bismuth Subnitrate responds to the tests for *Bismuth*, page 808, and for *Nitrate*, page 809.

Loss on drying, page 814—Dry Bismuth Subnitrate at 105° for 2 hours: it loses not more than 3 percent of its weight.

Carbonate—Add 3 g. of Bismuth Subnitrate to 3 ml. of warm nitric acid: no effervescence occurs. Pour the solution into 100 ml. of water: a white precipitate forms. Filter, evaporate the filtrate on a steam bath to 30 ml., again filter the liquid, divide the latter filtrate into portions of 5 ml. each, and use these several portions in the tests for *Chloride, Sulfate, Copper, Lead,* and *Silver*.

Chloride, page 784—A 10-ml. portion of the test liquid retained in the test for *Carbonate* shows no more chloride than corresponds to 0.5 ml. of 0.02 *N* hydrochloric acid (0.035 percent).

Sulfate—To a 5-ml. portion of the test liquid retained in the test for *Carbonate* add 5 drops of barium nitrate T.S.: no turbidity is produced immediately.

Alkalies and alkaline earths—Boil 1 g. of Bismuth Subnitrate with 20 ml. of a mixture of equal volumes of acetic acid and water, cool, and filter. Add 2 ml. of diluted hydrochloric acid, precipitate the bismuth by the addition of hydrogen sulfide, boil the mixture, and filter it. Add 5 drops of sulfuric acid to the filtrate, evaporate it to dryness, and ignite to constant weight: the weight of the residue does not exceed 5 mg. (0.5 percent).

Ammonium salts—Boil about 100 mg. of Bismuth Subnitrate with 5 ml. of sodium hydroxide T.S.: the vapor does not turn moistened red litmus blue.

Arsenic—Mix 1.25 g. of Bismuth Subnitrate with 5 ml. of water, cautiously add 2 ml. of sulfuric acid, heat the mixture until fumes of sulfur trioxide are copiously evolved. Cool, cautiously add 10 ml. of water, and again evaporate to strong fuming, repeating if necessary to remove any trace of nitric acid. Cool, and cautiously dilute with water to 35 ml. This solution meets the requirements of the *Arsenic Test*, page 777 (8 parts per million As).

Copper—To a 5-ml. portion of the test liquid retained in the test for *Carbonate* add a slight excess of ammonia T.S.: the liquid does not exhibit a bluish color.

Lead—Mix a 5-ml. portion of the test liquid retained in the test for *Carbonate* with an equal volume of diluted sulfuric acid: the liquid does not become cloudy.

Silver—To a 5-ml. portion of the test liquid retained in the test for *Carbonate* add hydrochloric acid, dropwise: no precipitate is formed which is insoluble in a slight excess of hydrochloric acid, but soluble in ammonia T.S.

Assay—Weigh accurately in a porcelain crucible about 1 g. of Bismuth Subnitrate, previously dried at 105° for 2 hours, and ignite to constant weight. From the weight of Bi_2O_3 so obtained determine the percentage in the sample taken.

Packaging and storage—Preserve Bismuth Subnitrate in well-closed containers.

CATEGORY—Antacid.

USUAL DOSE—See Milk of Bismuth.

Bitter Orange Peel, page 499

Blood Group Specific Substances A and B

Blood Group Specific Substances A and B is a sterile, isotonic solution of the polysaccharide-containing complexes that are capable of reducing the titer of the anti-A and the anti-B isoagglutinins of group O blood. The blood group specific substance A is usually isolated from hog gastric mucin and the blood group specific substance B is usually isolated from the glandular portion of horse gastric mucosa. Blood Group Specific Substances A and B contains a suitable preservative.

Description—Blood Group Specific Substances A and B is a clear solution, which may have a slight odor due to the preservative.

pH, page 824—The pH of Blood Group Specific Substances A and B is between 6.0 and 6.8.

Other requirements—Blood Group Specific Substances A and B complies with the requirements under *Biologics*, page 781, and with the identity, pyrogen, safety, sterility, potency, nonanaphylactic and other requirements of the U. S. Public Health Service.

Packaging and storage—Preserve Blood Group Specific Substances A and B in single-dose containers, at a temperature between 2° and 8°. Dispense it in the unopened container in which it was placed by the manufacturer.

Expiration date—The expiration date for Blood Group Specific Substances A and B is not more than 2 years after date of manufacture or date of issue.

Size available—Blood Group Specific Substances A and B is usually available in the following amount: 10 ml. (to be added to 500 ml. of group O blood).

CATEGORY—Blood neutralizer (isoagglutinins, group O blood).

USUAL DOSE—Intravenous, one transfusion unit (10 ml.) in approximately 500 ml. of group O blood.

Boric Acid

H_3BO_3 Mol. wt. 61.83

Boric Acid contains not less than 99.5 percent and not more than 100.5 percent of H_3BO_3, calculated on the dried basis.

Description—Boric Acid occurs as colorless, odorless scales of a somewhat pearly luster, as crystals, or as a white powder that is slightly unctuous to the touch. It is stable in air.

Solubility—Boric Acid is soluble in water and in alcohol. It is freely soluble in glycerin, in boiling water, and in boiling alcohol.

Completeness of solution—One g. of Boric Acid dissolves in 25 ml. of water, producing a clear solution.

Solubility in alcohol—One g. of Boric Acid dissolves completely in 10 ml. of boiling alcohol.

Identification—Boric Acid responds to the tests for *Borate*, page 808.

Loss on drying, page 814—Dry Boric Acid over silica gel for 5 hours: it loses not more than 0.5 percent of its weight.

Arsenic—A solution of 1.25 g. of Boric Acid in water meets the requirements of the *Arsenic test*, page 777 (8 parts per million As).

Heavy metals, page 806—Dissolve 1 g. of Boric Acid in 23 ml. of water, and add 2 ml. of diluted acetic acid: the heavy metals limit is 20 parts per million.

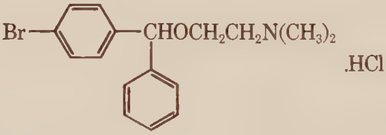
Assay—Dissolve about 2 g. of Boric Acid, accurately weighed, in 100 ml. of a mixture of equal volumes of glycerin and water, previously neutralized to phenolphthalein T.S., and titrate with 1 *N* sodium hydroxide. Discharge the pink color by the addition of 50 ml. of glycerin, neutralized to phenolphthalein T.S., and continue the titration until the pink color reappears. Each ml. of 1 *N* sodium hydroxide is equivalent to 61.83 mg. of H_3BO_3.

Labeling—The container label bears a warning that Boric Acid is not for internal use.

Packaging and storage—Preserve Boric Acid in well-closed containers.

CATEGORY—Buffer.

Bromodiphenhydramine Hydrochloride*



2-[(*p*-Bromo-α-phenylbenzyl)oxy]-*N*,*N*-dimethylethylamine Hydrochloride

$C_{17}H_{20}BrNO.HCl$ Mol. wt. 370.72

Bromodiphenhydramine Hydrochloride contains not less than 98.0 percent and not more than 101.0 percent of $C_{17}H_{20}BrNO.HCl$, calculated on the dried basis.

Description—Bromodiphenhydramine Hydrochloride occurs as a white to pale buff, crystalline powder, having no more than a faint odor.

Solubility—Bromodiphenhydramine Hydrochloride is freely soluble in water and in alcohol. It is soluble in isopropyl alcohol, and insoluble in ether and in solvent hexane.

Melting range, *Class Ia*, page 815—Bromodiphenhydramine Hydrochloride melts between 148° and 152°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Bromodiphenhydramine Hydrochloride, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Bromodiphenhydramine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 67,000 solution of Bromodiphenhydramine Hydrochloride in 0.1 *N* sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Bromodiphenhydramine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 230 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Bromodiphenhydramine Hydrochloride at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Assay—Dissolve about 700 mg. of Bromodiphenhydramine Hydrochloride, accurately weighed, in 50 ml. of glacial acetic acid, and add 10 ml. of benzene and 15 ml. of mercuric acetate T.S. Add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 37.07 mg. of $C_{17}H_{20}BrNO.HCl$.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Bromodiphenhydramine Hydrochloride in tight containers.

CATEGORY—Antihistaminic.

USUAL DOSE—**25 mg.** three times daily.

USUAL DOSE RANGE—**25** to **50 mg.**

Bromodiphenhydramine Hydrochloride Capsules

Bromodiphenhydramine Hydrochloride Capsules contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{17}H_{20}BrNO.HCl$.

Identification—Transfer the final solution obtained in the *Assay* to a separator, add about 1 ml. of 0.1 *N* sulfuric acid, and shake with 25 ml. of ether. (Methyl red enters the ether phase.) Drain the aqueous layer into another separator, add 5 ml. of sodium hydroxide T.S., and shake with 10 ml. of chloroform. Drain the chloroform layer into a small flask containing 2 g. of anhydrous sodium sulfate, and swirl. Pour the chloroform solution through a small cotton pledget, prerinsed with chloroform, into a beaker and evaporate to about 5 ml. Apply a few drops of the solution directly to a potassium bromide plate, and completely remove the chloroform by warming for 2 to 3 minutes under an infrared lamp: the infrared absorption spectrum of the bromodiphenhydramine base so prepared exhibits maxima at the same wavelengths as that of a similar preparation obtained from NF Bromodiphenhydramine Hydrochloride Reference Standard, similarly measured.

Content uniformity, *Method II*, page 798—Bromodiphenhydramine Hydrochloride Capsules meet the requirements of the content uniformity test for capsules using the following special procedure: Transfer as completely as possible the contents of one capsule to a suitable small flask, add a quantity of alcohol, accurately measured, to yield a concentration of about 50 mg. of bromodiphenhydramine hydrochloride per 100 ml., stopper securely, and mix thoroughly by swirling intermittently for a few minutes. Centrifuge a portion of the mixture at about 2000 r.p.m. until the solution becomes clear. Pipet 3.0 ml. of the supernatant liquid into a 100-ml. volumetric flask containing 10 ml. of 1 *N* sulfuric acid, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Bromodiphenhydramine Hydrochloride Reference Standard, in a mixture of 1 *N* sulfuric acid in alcohol (1 in 10), at a concentration of about 15 mcg. per ml., in 1-cm. cells, at the maximum at about 230 mμ, with a suitable spectrophotometer, using the 1 *N* sulfuric acid in alcohol (1 in 10) solution as the blank. Calculate the quantity, in mg., of $C_{17}H_{20}BrNO.HCl$ in the Capsule by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of bromodiphenhydramine hydrochloride in the capsule; D is the exact concentration, in mcg. per ml., of bromodiphenhydramine hydrochloride in the sample solution based upon the labeled quantity per capsule and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—

Chromatographic column—Pack a small pledget of cotton in the base of a 2.5 × 25-cm. chromatographic tube equipped with a stopcock. Thoroughly mix 7.5 g. of purified siliceous earth with 5 ml. of water, transfer the mixture to the tube, and tamp gently to compress the material into a uniform mass.

Assay preparation—Remove as completely as possible the contents of not less than 20 Bromodiphenhydramine Hydrochloride Capsules, and weigh. Mix, and transfer an accurately weighed portion of the powder, equivalent to about 250 mg. of bromodiphenhydramine hydrochloride, to a 250-ml. beaker. Add 4 ml. of water, mix, add 1 ml. of 2 *N* sodium hydroxide, and mix. Add 10 g. of purified siliceous earth, and intimately mix by kneading with a flexible spatula until the mixture is fluffy.

Procedure—Transfer the *Assay preparation* to the column in divided portions, and tamp the column gently to compress the material into a uniform mass. Rinse the beaker in which the *Assay preparation* was prepared with a mixture of 3 g. of purified siliceous earth and 2 ml. of water, transfer to the column, and tamp to compress. Place a thin layer of cotton on top of the column, and pass ether through the column at a rate of 2 to 4 ml. per minute, collecting 75 ml. of eluate in a 125-ml. separator. Extract the eluate with 10.0 ml. of 0.1 *N* sulfuric acid followed by two 5-ml. portions of water, and combine the extracts in a conical flask. To the flask add 3 drops of methyl red T.S., and titrate the excess acid with 0.02 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sulfuric acid is equivalent to 37.07 mg. of $C_{17}H_{20}BrNO.HCl$.

Packaging and storage—Preserve Bromodiphenhydramine Hydrochloride Capsules in tight containers.

Capsules available—Bromodiphenhydramine Hydrochloride Capsules usually available contain the following amount of bromodiphenhydramine hydrochloride: 25 mg.

CATEGORY and DOSE—See Bromodiphenhydramine Hydrochloride.

Bromodiphenhydramine Hydrochloride Elixir

Bromodiphenhydramine Hydrochloride Elixir contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{17}H_{20}BrNO.HCl$.

Identification—Proceed as directed for *Identification* under *Bromodiphenhydramine Hydrochloride Capsules,* page 105.

Assay—Evaporate an accurately measured volume of Bromodiphenhydramine Hydrochloride Elixir, equivalent to about 250 mg. of bromodiphenhydramine hydrochloride, to about half the original volume, using a suitable vacuum evaporator. Transfer the concentrated solution to a 250-ml. separator, with the aid of sufficient warm water to bring the volume to the original volume. Add 20 g. of sodium chloride, and shake until dissolved. Add 5 ml. of sodium hydroxide T.S., shake with 100 ml. of ether, and drain the aqueous layer into a second separator containing 50 ml. of ether. Shake, and discard the aqueous layer. Wash the ether solutions with two 20-ml. portions of water, shaking each aqueous portion successively in the two separators, and then discard the aqueous solutions. Extract the ether solutions successively with 10.0 ml. of 0.1 *N* sulfuric acid, followed by two 5-ml. portions of water, and collect the aqueous extracts in a conical flask. Add 3 drops of methyl red T.S. to the solution in the flask, and titrate the excess acid with 0.02 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sulfuric acid is equivalent to 37.07 mg. of $C_{17}H_{20}BrNO.HCl$.

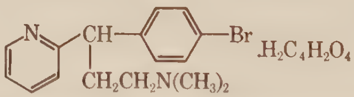
Alcohol content, page 772—Bromodiphenhydramine Hydrochloride Elixir contains from 12 to 15 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Bromodiphenhydramine Hydrochloride Elixir in tight, light-resistant containers.

Elixir available—Bromodiphenhydramine Hydrochloride Elixir usually available contains the following amount of bromodiphenhydramine hydrochloride: 12.5 mg. in 5 ml.

CATEGORY and DOSE—See Bromodiphenhydramine Hydrochloride.

Brompheniramine Maleate



2-[*p*-Bromo-α-[2-(dimethylamino)ethyl]benzyl]pyridine Maleate (1:1)

$C_{16}H_{19}BrN_2.C_4H_4O_4$ Mol. wt. 435.32

Brompheniramine Maleate, dried at 105° for 3 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{16}H_{19}BrN_2.C_4H_4O_4$.

Description—Brompheniramine Maleate occurs as a white, odorless, crystalline powder.

Solubility—Brompheniramine Maleate is freely soluble in water, and is soluble in alcohol and in chloroform. It is slightly soluble in ether and in benzene.

Melting range, page 814—Brompheniramine Maleate melts between 130° and 135°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Brompheniramine Maleate, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Brompheniramine Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 30,000 solution of Brompheniramine Maleate in methanol exhibits maxima and minima at the same wavelengths as that of NF Brompheniramine Maleate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 262 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Brompheniramine Maleate (1 in 100) is between 4.0 and 5.0.

Loss on drying, page 814—Dry Brompheniramine Maleate at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Brompheniramine Maleate yields not more than 0.15 percent of residue on ignition.

Assay—Dissolve about 425 mg. of Brompheniramine Maleate, previously dried at 105° for 3 hours and accurately weighed, in 50 ml. of glacial acetic acid. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 21.77 mg. of $C_{16}H_{19}BrN_2.C_4H_4O_4$.

Packaging and storage—Preserve Brompheniramine Maleate in tight, light-resistant containers.

CATEGORY—Antihistaminic.

USUAL DOSE—Oral, **4 mg.** one to four times a day.

USUAL DOSE RANGE—**4** to **8 mg.**

Brompheniramine Maleate Elixir

Brompheniramine Maleate Elixir contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{16}H_{19}BrN_2.C_4H_4O_4$.

Identification—Transfer a volume of Brompheniramine Maleate Elixir, equivalent to about 50 mg. of brompheniramine maleate, to a separator, make distinctly alkaline with sodium hydroxide T.S., and extract with two 50-ml. portions of chloroform, shaking gently to avoid emulsification. Wash the combined chloroform extracts with 10 ml. of water, wash the latter with 20 ml. of chloroform, and discard the aqueous phase. Filter the combined chloroform extracts into a conical flask, and evaporate the solvent on a steam bath, with the aid of a current of air. To the residue add 25 ml. of 0.01 *N* hydrochloric acid, and proceed as directed under *Identification—Organic Nitrogenous Bases*, page 810, beginning with "Transfer the liquid to a separator. . . .": the Elixir meets the requirements of the test.

pH, page 824—The pH of Brompheniramine Maleate Elixir is between 2.5 and 3.5.

Assay—Transfer an accurately measured volume of Brompheniramine Maleate Elixir, equivalent to about 20 mg. of brompheniramine maleate, to a separator, make distinctly alkaline with sodium hydroxide T.S., and extract with ten 10-ml. portions of chloroform, shaking gently to avoid emulsification. Wash the combined chloroform extracts with 10 ml. of water, wash the latter with 20 ml. of chloroform, and discard the aqueous phase. Quantitatively filter the combined chloroform extracts and washing into a conical flask, and evaporate the solvent on a steam bath, with the aid of a current of air. To the residue add 25 ml. of glacial acetic acid and 5 ml. of acetic anhydride, agitate, and allow to stand for about 15 minutes. Add 1 drop of crystal violet T.S., and titrate with 0.01 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* perchloric acid is equivalent to 2.177 mg. of $C_{16}H_{19}BrN_2.C_4H_4O_4$.

Alcohol content, page 772—Brompheniramine Maleate Elixir contains from 2.7 to 3.3 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Brompheniramine Maleate Elixir in well-closed, light-resistant containers.

Elixir available—Brompheniramine Maleate Elixir usually available contains the following amount of brompheniramine maleate: 2 mg. in 5 ml.

CATEGORY AND DOSE—See Brompheniramine Maleate.

Brompheniramine Maleate Tablets

Brompheniramine Maleate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{16}H_{19}BrN_2.C_4H_4O_4$.

Identification—Brompheniramine Maleate Tablets meet the requirements under *Identification—Organic Nitrogenous Bases,* page 810.

Disintegration, page 878—The disintegration time limit for Brompheniramine Maleate Tablets, determined in simulated gastric fluid T.S., is 30 minutes.

Content uniformity, *Method I,* page 799—Brompheniramine Maleate Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 30 Brompheniramine Maleate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 80 mg. of brompheniramine maleate, to a 200-ml. volumetric flask, add 10 ml. of water, and warm on a steam bath until the powder has formed a wet paste. Add 10 ml. of diluted hydrochloric acid, dilute to volume with water, and mix. Transfer 20.0 ml. to a separator, add 5 ml. of sodium hydroxide T.S., and extract with five 35-ml. portions of chloroform. Combine the extracts in a 200-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Brompheniramine Maleate Reference Standard, in the same medium, at a concentration of about 40 mcg. per ml., in 1-cm. cells, at the maximum, at about 263 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{16}H_{19}BrN_2 \cdot C_4H_4O_4$ in the portion of Tablets taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

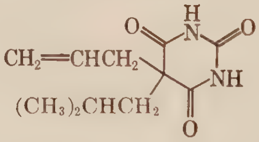
Packaging and storage—Preserve Brompheniramine Maleate Tablets in tight containers.

Tablets available—Brompheniramine Maleate Tablets usually available contain the following amount of brompheniramine maleate: 4 mg.

Category and Dose—See Brompheniramine Maleate.

Butabarbital, Sodium, page 637
Butabarbital, Sodium, Capsules, page 638
Butabarbital, Sodium, Elixir, page 639
Butabarbital, Sodium, Tablets, page 639

Butalbital



5-Allyl-5-isobutylbarbituric Acid

$C_{11}H_{16}N_2O_3$ Mol. wt. 224.26

Butalbital, dried at 105° for 2 hours, contains not less than 97.5 percent and not more than 101.5 percent of $C_{11}H_{16}N_2O_3$.

Description—Butalbital occurs as a white, crystalline powder. It is odorless, has a slightly bitter taste, and is stable in air. Its saturated solution is acid to litmus.

Solubility—Butalbital is freely soluble in alcohol, in ether, and in chloroform. It is slightly soluble in cold water and soluble in boiling water. It is soluble in solutions of fixed alkalies and alkali carbonates.

Melting range, page 814—Butalbital melts between 137° and 140°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Butalbital, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Butalbital Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Butalbital in 0.1 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Butalbital Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 245 mμ, do not differ by more than 2.5 percent.

Loss on drying, page 814—Dry

Butalbital at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Butalbital yields not more than 0.1 percent of residue on ignition.

Heavy metals, page 806—Boil about 100 mg. of Butalbital with 10 ml. of water for 2 minutes, cool, and filter. Add 10 ml. of hydrogen sulfide T.S. to the filtrate: no color or precipitate is produced.

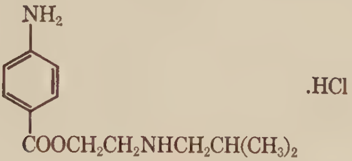
Readily carbonizable substances, page 856—Dissolve about 500 mg. of Butalbital in 5 ml. of sulfuric acid T.S.: the solution has no more color than *Matching Fluid A.*

Assay—Dissolve about 300 mg. of Butalbital, previously dried at 105° for 2 hours and accurately weighed, in 10 ml. of alcohol, add 10 ml. of water, and titrate to the first faint blue color with 0.1 *N* sodium hydroxide, using thymolphthalein T.S. as the indicator. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 22.43 mg. of $C_{11}H_{16}N_2O_3$.

Packaging and storage—Preserve Butalbital in well-closed containers.

CATEGORY—Sedative.
USUAL DOSE—**50 mg.** every 6 hours.
USUAL DOSE RANGE—**50** to **100 mg.**

Butethamine Hydrochloride



2-(Isobutylamino)ethanol *p*-Aminobenzoate (Ester) Monohydrochloride

$C_{13}H_{20}N_2O_2 . HCl$ Mol. wt. 272.78

Butethamine Hydrochloride, dried at 105° for 2 hours, contains not less than 98.5 percent and not more than 100.5 percent of $C_{13}H_{20}N_2O_2 . HCl$.

Description—Butethamine Hydrochloride occurs as small, white crystals, or as a white, crystalline powder. It is odorless, and is stable in air. Butethamine Hydrochloride exhibits local anesthetic properties when placed upon the tongue. The pH of a 1 in 100 solution is about 5.

Solubility—Butethamine Hydrochloride is sparingly soluble in water, slightly soluble in alcohol and in chloroform, very slightly soluble in benzene, and practically insoluble in ether.

Identification—

A: To 5 ml. of Butethamine Hydrochloride solution (1 in 500) add 1 ml. of silver nitrate T.S.: a curdy, white precipitate, insoluble in nitric acid but soluble in ammonia T.S., separates.

B: To 5 ml. of Butethamine Hydrochloride solution (1 in 500) add 0.5 ml. of diluted hydrochloric acid and 0.5 ml. of a solution of sodium nitrite (1 in 10), followed by 200 mg. of betanaphthol dissolved in 10 ml. of ammonia T.S.: an orange precipitate forms which is soluble in ether.

C: To 2 ml. of Butethamine Hydrochloride solution (1 in 500) add 1 ml. of mercuric-potassium iodide T.S.: a white precipitate forms.

Melting range, page 814—Butethamine Hydrochloride melts between 193° and 197°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Butethamine Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Butethamine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Butethamine Hydrochloride exhibits maxima and minima at the same wavelengths as that of NF Butethamine Hydrochloride Reference Standard, similarly measured.

Loss on drying, page 814—Dry Butethamine Hydrochloride at 105° for 2 hours: it loses not more than 0.2 percent of its weight.

Residue on ignition, page 858—Butethamine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 200 mg. of Butethamine Hydrochloride, previously dried at 105° for 2 hours and accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix. Pipet 10.0 ml. of this solution into a 1000-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Butethamine Hydrochloride Reference Standard, previously dried at 105° for 2 hours, in water at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 290 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2.HCl$ in the Butethamine Hydrochloride taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Butethamine Hydrochloride in well-closed containers.

Category—Local anesthetic (dental).

Usual dose—Local injection **1.8** to **2.2 ml.** of a 1.5% solution with epinephrine 1:100,000 or a 2% solution with epinephrine 1:50,000.

Butethamine Hydrochloride and Epinephrine Injection

Butethamine Hydrochloride and Epinephrine Injection is a sterile solution of butethamine hydrochloride and epinephrine in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O_2.HCl$ (butethamine hydrochloride) and not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (epinephrine).

Identification—Butethamine Hydrochloride and Epinephrine Injection responds to *Identification test B* under *Butethamine Hydrochloride,* page 109.

Other requirements—Butethamine Hydrochloride and Epinephrine Injection meets the requirements under *Injections,* page 810.

pH, page 824—The pH of Butethamine Hydrochloride and Epinephrine Injection is between 3.3 and 5.5.

Assay for butethamine hydrochloride—

Standard preparation—Weigh accurately about 20 mg. of NF Butethamine Hydrochloride Reference Standard, previously dried at 105° for 2 hours, transfer to a 1000-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer to a separator an accurately measured volume of Butethamine Hydrochloride and Epinephrine Injection, equivalent to about 200 mg. of butethamine hydrochloride, add 3 ml. of ammonia T.S., and completely extract the butethamine by shaking with successive portions of chloroform. Filter the chloroform extracts into a beaker, wash the filter with chloroform, and evaporate the combined filtrate and washings in a current of warm air nearly to dryness. To the residue add 30 ml. of 0.1 *N* hydrochloric acid, heat on a steam bath until the odor of chloroform is no longer perceptible, cool, transfer quantitatively to a 100-ml. volumetric flask, dilute to volume with water, and mix. Pipet 10.0 ml. of this solution into a 1000-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Determine the absorbance of each solution, in 1-cm. cells, at the maximum at about 290 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2.HCl$ in each ml. of the Injection taken by the formula $10 \times (C/V) \times (A_U/A_S)$, in which A_U is the absorbance of the *Assay preparation,* A_S is that of the *Standard preparation,* C is the exact concentration, in mcg. per ml., of the *Standard preparation* and V is the volume, in ml., of the Injection taken.

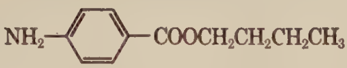
Assay for epinephrine—Proceed as directed under *Epinephrine Assay,* page 803.

Packaging and storage—Preserve Butethamine Hydrochloride and Epinephrine Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Butethamine Hydrochloride and Epinephrine Injection usually available contains the following amounts of butethamine hydrochloride and epinephrine: 1 percent butethamine hydrochloride and 1 in 75,000 epinephrine in 5-ml. cartridges; 1.5 percent butethamine hydrochloride and 1 in 100,000 epinephrine in 5-ml. cartridges; and in 30-ml. bottles; 1.5 percent butethamine hydrochloride and 1 in 30,000 epinephrine in 5-ml. cartridges; 2 percent butethamine hydrochloride and 1 in 50,000 epinephrine in 1.8-, 2-, 2.2-, and 2.5-ml. cartridges; in 2-ml. ampuls; and in 30-, 60-, and 125-ml. bottles.

Category and Dose—See Butethamine Hydrochloride.

Butyl Aminobenzoate



Butyl *p*-Aminobenzoate

$C_{11}H_{15}NO_2$ Mol. wt. 193.25

Butyl Aminobenzoate, dried over phosphorus pentoxide for 3 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_{11}H_{15}NO_2$.

Description—Butyl Aminobenzoate occurs as a white, crystalline powder. It is odorless and tasteless.

Solubility—Butyl Aminobenzoate is very slightly soluble in water. It is soluble in dilute acids, in alcohol, in chloroform, in ether, and in fixed oils. It is slowly hydrolyzed when boiled with water.

Identification—

A: Add a few drops of a solution of sodium nitrite (1 in 10) to 2 ml. of a solution of Butyl Aminobenzoate in 0.1 *N* hydrochloric acid (1 in 100), and add the mixture to a solution of 200 mg. of beta-naphthol in 10 ml. of a solution of sodium hydroxide (1 in 10): a scarlet red precipitate is produced.

B: To 1 ml. of a solution of Butyl Aminobenzoate in 0.1 *N* hydrochloric acid (1 in 100) add a few drops of iodine T.S., shake the mixture, and allow it to stand for 10 minutes with occasional shaking: a dark brown precipitate is formed which changes into large, reddish brown prisms (under the same conditions *benzocaine* gives lustrous scales).

Melting range, page 814—Butyl Aminobenzoate melts between 57° and 59°.

Residue on ignition, page 858—Butyl Aminobenzoate yields not more than 0.15 percent of residue on ignition.

Reaction—Dissolve 1 g. of Butyl Aminobenzoate in 10 ml. of neutralized alcohol: a clear solution results. Dilute this solution with 10 ml. of water, add 2 drops of phenolphthalein T.S. and 1 drop of 0.1 *N* sodium hydroxide: a red color is produced.

Loss on drying, page 814—Dry Butyl Aminobenzoate over phosphorus pentoxide for 3 hours: it loses not more than 1 percent of its weight.

Completeness and color of solution—One g. of Butyl Aminobenzoate dissolves completely in 30 ml. of alcohol and in 30 ml. of ether, and the solutions are colorless.

Chloride—To a solution of 200 mg. of Butyl Aminobenzoate in 10 ml. of alcohol add 1 ml. of diluted nitric acid and a few drops of silver nitrate T.S.: no turbidity is produced.

Heavy metals, page 806—Dissolve 1 g. of Butyl Aminobenzoate in 2 ml. of diluted acetic acid and sufficient alcohol to make 25 ml.: the heavy metals limit for Butyl Aminobenzoate is 10 parts per million.

Assay—Dissolve about 400 mg. of Butyl Aminobenzoate, previously dried over phosphorus pentoxide for 3 hours and accurately weighed, in a mixture of 100 ml. of water and 20 ml. of hydrochloric acid. Cool the solution in an ice bath to about 10°, and titrate with 0.1 *M* sodium nitrite until a blue color is produced immediately when the titrated solution is spotted on starch iodide paper. When the titration is complete, the end-point is reproducible after the mixture has been allowed to stand for 5 minutes. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 19.32 mg. of $C_{11}H_{15}NO_2$.

Packaging and storage—Preserve Butyl Aminobenzoate in well-closed containers.

CATEGORY—Local anesthetic.

Caffeine and Ergotamine Tartrate Suppositories, page 268
Caffeine and Ergotamine Tartrate Tablets, page 270
Caffeine, Phenacetin, and Aspirin Tablets, page 68
Caffeine, Phenacetin, Aspirin, and Codeine Phosphate Tablets, page 178

Citrated Caffeine

Citrated Caffeine is a mixture of caffeine and citric acid containing, when dried at 80° for 4 hours, not less than 48.0 percent and not more than 52.0 percent of $C_8H_{10}N_4O_2$ (anhydrous caffeine), and not less than 48.0 percent and not more than 52.0 percent of $C_6H_8O_7$ (anhydrous citric acid). The sum of the percentages of anhydrous caffeine and anhydrous citric acid is not less than 98.5 and not more than 101.0.

Description—Citrated Caffeine occurs as a white, odorless powder, having a slightly bitter, acid taste. Its solutions are acid to litmus.

Solubility—Citrated Caffeine is freely soluble in warm water. On diluting the solution with an equal volume of water, a portion of the caffeine gradually separates, but redissolves on the further addition of water.

Identification—

A: Dissolve about 20 mg. of Citrated Caffeine in 1 ml. of hydrochloric acid in a porcelain dish, add 100 mg. of potassium chlorate, and evaporate to dryness on a steam bath. Invert the dish over a vessel containing a few drops of ammonia T.S.: the residue acquires a purple color, which disappears upon the addition of a solution of a fixed alkali.

B: Dissolve about 100 mg. of Citrated Caffeine in 10 ml. of water, and add 1 ml. of calcium chloride T.S. and 3 drops of bromothymol blue T.S. Add 0.1 *N* sodium hydroxide, dropwise, until the color of the solution just changes to a clear blue, then boil the solution gently for 3 minutes, agitating it gently during the heating period: a white, crystalline precipitate appears in the liquid.

C: Add 1 ml. of mercuric sulfate T.S. to 5 ml. of a solution of Citrated Caffeine (1 in 100), heat the mixture to boiling, and add 1 ml. of potassium permanganate T.S.: a white precipitate appears.

D: The residue obtained in the *Assay for caffeine*, when recrystallized from hot water and dried at 80° for 4 hours, melts between 235° and 237.5°, page 814.

Loss on drying, page 814—Dry Citrated Caffeine at 80° for 4 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Citrated Caffeine yields not more than 0.1 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Citrated Caffeine in 15 ml. of water, and dilute to 25 ml. with water: the heavy metals limit for Citrated Caffeine is 15 parts per million.

Readily carbonizable substances, page 856—Heat a mixture of 250 mg. of Citrated Caffeine and 5 ml. of sulfuric acid T.S. in a porcelain dish on a steam bath for 15 minutes, protecting it from dust: the solution has no more color than Matching Fluid K.

Assay for caffeine—Accurately weigh about 1 g. of Citrated Caffeine, previously dried at 80° for 4 hours, and dissolve it in 10 ml. of hot water. Add 8 ml. of sodium hydroxide T.S., cool the solution, and shake it in a separator with three or more successive 20-ml. portions of chloroform to effect complete extraction of the caffeine. Filter the combined chloroform solutions through a small filter, previously moistened with chloroform, into a tared dish. Wash the stem of the separator, the filter, and the funnel with 10 ml. of hot chloroform, adding the washings to the dish, and evaporate the combined chloroform solutions on a steam bath, adding 2 ml. of alcohol just before the last trace of chloroform is expelled. Complete the evaporation of the solvent, and dry the residue consisting of $C_8H_{10}N_4O_2$ at 80° for 4 hours, and weigh.

Assay for citric acid—Weigh accurately about 400 mg. of Citrated Caffeine, previously dried at 80° for 4 hours, and dissolve it in 25 ml. of water. Add 3 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to a faint pink color. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 6.404 mg. of $C_6H_8O_7$.

Packaging and storage—Preserve Citrated Caffeine in tight containers.

CATEGORY—Central stimulant.
USUAL DOSE—**300 mg.** as necessary.
USUAL DOSE RANGE—**100** to **500 mg.**

Citrated Caffeine Tablets

Citrated Caffeine Tablets contain an amount of $C_8H_{10}N_4O_2$ (anhydrous caffeine) equivalent to not less than 45.0 percent and not more than 55.0 percent of the labeled amount of citrated caffeine.

Identification—Citrated Caffeine Tablets respond to the *Identification tests* under *Citrated Caffeine*, page 111.

Disintegration, page 878–The disintegration time limit for Citrated Caffeine Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Citrated Caffeine Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 200-ml.

volumetric flask, add 100 ml. of chloroform, and shake mechanically for 30 minutes. Dilute to volume with chloroform, mix and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with chloroform to provide a solution containing approximately 7.5 mcg. of anhydrous caffeine per ml. Concomitantly determine the absorbance of this solution and of a standard solution of NF Caffeine Reference Standard, in the same medium, at a concentration of about 7.5 mcg. per ml., in 1-cm. cells, at the maximum at about 276 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_8H_{10}N_4O_2$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of anhydrous caffeine, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the standard solution.

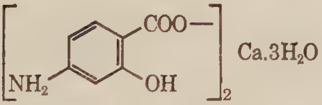
Assay—Weigh and finely powder not less than 20 Citrated Caffeine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg. of citrated caffeine, to a separator, and dissolve it, as completely as possible, in 10 ml. of water. Add 1 drop of phenolphthalein T.S., then add sodium hydroxide T.S. until a permanent pink color is produced. Extract the caffeine completely from the mixture with successive portions of chloroform, pass each portion through a filter which has been previously moistened with chloroform, and wash the stem of the funnel and the filter with a few ml. of hot chloroform. Evaporate the filtrate on a steam bath, adding 2 ml. of alcohol just before the chloroform is all evaporated. Complete the evaporation, and dry the residue at 80° for 4 hours. The weight of residue obtained represents the yield of $C_8H_{10}N_4O_2$.

Packaging and storage—Preserve Citrated Caffeine Tablets in tight containers.

Tablets available—Citrated Caffeine Tablets usually available contain the following amounts of citrated caffeine: 60 and 150 mg.

CATEGORY and DOSE—See Citrated Caffeine.

Calcium Aminosalicylate



Calcium 4-Aminosalicylate

$C_{14}H_{12}CaN_2O_6 \cdot 3H_2O$ Mol. wt. 398.39

Calcium Aminosalicylate contains not less than 98.0 percent and not more than 100.5 percent of $C_{14}H_{12}CaN_2O_6$, calculated on the anhydrous basis.

Caution: Prepare solutions of Calcium Aminosalicylate within 24 hours of administration. Under no circumstances use a solution if its color is darker than that of a freshly prepared solution.

Description—Calcium Aminosalicylate occurs as white to cream-colored crystals or powder. It is odorless and has an alkaline, slightly bitter-sweet taste. It is somewhat hygroscopic. Its solutions decompose slowly and darken in color.

Solubility—Calcium Aminosalicylate is freely soluble in water; it is slightly soluble in alcohol.

Identification—

A: Dissolve about 3 g. of Calcium Aminosalicylate in 50 ml. of water, and add acetic acid, dropwise, until the mixture is distinctly acid. Filter with suction, retaining the filtrate for *Identification test C*. Wash the precipitate with several small portions of water, and dry in vacuum over phosphorus pentoxide. Place about 1 g. of the aminosalicylic acid so obtained in a small, round-bottom flask, and add 10 ml. of acetic anhydride. Heat the flask on a steam bath for 30 minutes, add 40 ml. of water, mix, filter, and cool. Allow to stand until the diacetyl derivative has precipitated. Collect the precipitate on a filter, wash well with water, and dry at 105° for 1 hour: the diacetyl derivative so obtained melts between 191° and 197°, page 814.

B: Shake 100 mg. of the aminosalicylic acid obtained in *Identification test A* with 10 ml. of water, and filter. To 5 ml. of the filtrate add 1 drop of ferric chloride T.S.: a violet color is produced.

C: The filtrate obtained in *Identification test A* responds to the tests for *Calcium*, page 808.

Ultraviolet absorption, page 866—Dissolve 250 mg. of the aminosalicylic acid obtained in *Identification test A* in 3 ml. of sodium hydroxide T.S., transfer to a 500-ml. volumetric flask, add water to volume, and mix. Transfer a 5-ml. aliquot to a 250-ml. volumetric flask containing 12.5 ml. of pH 7 buffer (page 783), add water to volume, and mix. This solution, when compared in a suitable spectrophotometer against a blank of the same buffer in the same concentration, exhibits absorbance maxima at 265 ± 2 mμ and 299 ± 2 mμ, and the ratio A_{265}/A_{299} is between 1.50 and 1.56.

pH, page 824—The pH of a solution of Calcium Aminosalicylate (1 in 50) is between 6.0 and 8.0.

Water, page 900—Determine the water content of Calcium Aminosalicylate by the titrimetric method: it contains not less than 12.5 percent and not more than 14.5 percent of water.

Clarity of solution—A solution of 1 g. of Calcium Aminosalicylate in 50 ml. of water shows no more turbidity than that produced by adding 0.10 ml. of 0.02 *N* hydrochloric acid to a mixture of 48 ml. of water, 1 ml. of nitric acid, and 1 ml. of silver nitrate T.S., the comparisons being made in glass cylinders of the same internal diameter by viewing horizontally against a white and a black background.

Clarity of solution in diluted nitric acid—One g. of Calcium Aminosalicylate dissolves in a mixture of 5 ml. of nitric acid and 45 ml. of water to give a clear solution that has not more than a slight color.

Chloride, page 784—A 500-mg. portion of Calcium Aminosalicylate shows no more chloride than corresponds to 0.3 ml. of 0.02 *N* hydrochloric acid (0.042 percent).

Heavy metals, *Method II*, page 806—The heavy metals limit for Calcium Aminosalicylate is 30 parts per million.

Hydrogen sulfide and sulfur dioxide—Dissolve about 500 mg. of Calcium Aminosalicylate in 5 ml. of water, add 5 ml. of diluted hydrochloric acid, and stir vigorously: no odor of hydrogen sulfide or of sulfur dioxide is perceptible and there is not more than a faint odor of amyl alcohols. A piece of moistened lead acetate test paper held over the mixture does not become discolored.

***m*-Aminophenol**—Weigh accurately an amount, calculated on the basis of the *Assay*, of Calcium Aminosalicylate equivalent to 562 mg. of anhydrous calcium aminosalicylate (500 mg. of aminosalicylic acid), and transfer to a 100-ml. volumetric flask. Add 1.8 ml. of sodium hydroxide T.S., and dilute to about 80 ml. with water. Add 10 ml. of dilute sulfuric acid (1 in 10), add water to volume, and mix. Within 150 seconds from the time the acid is added, pipet 5.0 ml. of this solution into a second 100-ml. volumetric flask, immersed in an ice bath and containing 50 ml. of water at 0° to 5°, and add 2.5 ml. of sodium nitrite solution (1 in 100). Mix, and allow to stand in the ice bath for 3 minutes ± 5 seconds. Add 25 ml. of sodium carbonate T.S., mix, and place the flask in a water bath at 25° for 15 minutes. Add water to volume, mix, and allow the solution to stand at 25° for 3 hours. Determine the absorbance of the clear supernatant solution at the absorbance maximum observed in a range of 425 to 435 mμ in a 1-cm. cell, with a suitable spectrophotometer, using water as the blank. Calculate the percent of *m*-aminophenol by the formula $(A - 0.320)/1.09$, in which A is the absorbance of the solution, 0.320 is the absorbance correction factor representing color produced other than by the reaction of *m*-aminophenol initially present, and 1.09 is the factor converting absorbance to percent of *m*-aminophenol in Calcium Aminosalicylate: not more than 0.20 percent of *m*-aminophenol is found.

Assay—Dissolve about 350 mg. of Calcium Aminosalicylate, accurately weighed, in about 25 ml. of water, and allow to stand with occasional swirling for about 10 minutes. Add 25 ml. of glacial acetic acid and 20 ml. of potassium bromide solution (1 in 4). Cool to 15°, add 5 ml. of hydrochloric acid, and immediately titrate with 0.1 *M* sodium nitrite, stirring vigorously, determining the end-point electrometrically using suitable electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 17.22 mg. of $C_{14}H_{12}CaN_2O_6$.

Packaging and storage—Preserve Calcium Aminosalicylate in tight, light-resistant containers.

CATEGORY—Antibacterial (tuberculostatic).

USUAL DOSE—**4 g.** four times a day.

USUAL DOSE RANGE—**10** to **25 g.** daily in 4 divided doses.

Calcium Aminosalicylate Capsules

Calcium Aminosalicylate Capsules contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{14}H_{12}CaN_2O_6 . 3H_2O$.

Identification—Digest the contents of a sufficient number of Calcium Aminosalicylate Capsules, equivalent to about 3 g. of calcium aminosalicylate, with 50 ml. of water, and filter. Add 15 ml. of diluted acetic acid to the filtrate and allow to stand until precipitation has occurred. Collect the precipitate on a filter, wash well with water, and dry at 105° for 30 minutes: the residue responds to *Identification tests A* and *B* and the test for *Ultraviolet absorption* under *Calcium Aminosalicylate*, page 113, and the filtrate responds to the tests for *Calcium*, page 808.

Weight variation, page 901—Calcium Aminosalicylate Capsules meet the requirements of the weight variation test for capsules.

***m*-Aminophenol**—Transfer an accurately weighed portion, calculated on the basis of the *Assay*, of the contents of Calcium Aminosalicylate Capsules, equivalent to 1.300 g. of calcium aminosalicylate (1 g. of aminosalicylic acid), to a 100-ml. volumetric flask, and dissolve the soluble portion in about 50 ml. of water. Add water to volume, mix, and filter, discarding the first 15 ml. of filtrate. Pipet 50.0 ml. of the subsequent filtrate into a 100-ml. volumetric flask, and continue as directed in the test for *m-Aminophenol* under *Calcium Aminosalicylate*, page 113, beginning with "... dilute to about 80 ml. with water ...": not more than 0.77 percent of *m*-aminophenol is found.

Assay—Transfer as completely as possible the contents of not less than 20 Calcium Aminosalicylate Capsules to a suitable tared container, and determine the average weight per capsule. Mix the combined contents thoroughly, and transfer an accurately weighed portion, equivalent to about 400 mg. of calcium aminosalicylate, to a 150-ml. beaker. Add about 25 ml. of water, and allow to stand with occasional swirling for about 10 minutes, warming gently, if necessary to effect complete solution. Add 25 ml. of glacial acetic acid and 20 ml. of potassium bromide solution (1 in 4), and continue as directed in the *Assay* under *Calcium Aminosalicylate*, page 113, beginning with "Cool to 15° ... " Each ml. of 0.1 *M* sodium nitrite is equivalent to 19.92 mg. of $C_{14}H_{12}CaN_2O_6 . 3H_2O$.

Packaging and storage—Preserve Calcium Aminosalicylate Capsules in tight, light-resistant containers.

Capsules available—Calcium Aminosalicylate Capsules usually available contain the following amount of calcium aminosalicylate: 500 mg.

CATEGORY and DOSE—See Calcium Aminosalicylate.

Calcium Aminosalicylate Tablets

Calcium Aminosalicylate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{14}H_{12}CaN_2O_6 . 3H_2O$.

Identification—Digest a quantity of powdered Calcium Aminosalicylate Tablets, equivalent to about 3 g. of calcium aminosalicylate, with 50 ml. of water, and filter. Add 15 ml. of diluted acetic acid to the filtrate and allow to stand until precipitation has occurred. Collect the precipitate on a filter, wash well with water, and dry at 105° for 30 minutes: the residue responds to the *Identification tests A* and *B*, and the filtrate responds to *Identification test C* under *Calcium Aminosalicylate*, page 113.

Ultraviolet absorption—A portion of the residue obtained under *Identification* meets the requirements for *Ultraviolet absorption* under *Calcium Aminosalicylate*, page 113.

Disintegration, page 878—The disintegration time limit for Calcium Aminosalicylate Tablets is 30 minutes.

Weight variation, page 901—Calcium Aminosalicylate Tablets meet the requirements of the weight variation test for tablets.

***m*-Aminophenol**—Weigh accurately a quantity, calculated on the basis of the *Assay*, of powdered Calcium Aminosalicylate Tablets, equivalent to 1.300 g. of calcium aminosalicylate trihydrate (1.0 g. of aminosalicylic acid). Transfer the weighed sample to a 100-ml. volumetric flask, and dissolve the soluble portion in about 50 ml. of water. Add water to volume, mix, and filter. Pipet 50.0 ml. of the clear filtrate into a 100-ml. volumetric flask, and proceed as directed in the test for *m-Aminophenol* under *Calcium Aminosalicylate*, page 113, beginning with "...dilute to about 80 ml. with water...." Calculate the percent of *m*-aminophenol in the calcium aminosalicylate obtained from the Tablets by the formula (*A* − 0.320)/1.09 in which *A* is the absorbance of the solution, 0.320 is the absorbance correction factor representing color produced other than by the reaction of *m*-aminophenol initially present, and 1.09 is the factor converting absorbance to percent of *m*-aminophenol in calcium aminosalicylate: the calcium aminosalicylate obtained from the Tablets contains not more than 0.77 percent of *m*-aminophenol.

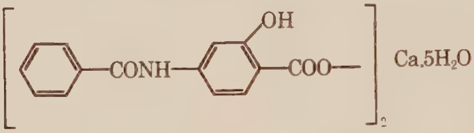
Assay—Weigh and finely powder not less than 20 Calcium Aminosalicylate Tablets. Weigh accurately a portion of the powder, equivalent to about 400 mg. of calcium aminosalicylate, transfer it to a wide-mouth, 250-ml. conical flask, add about 25 ml. of water, and shake the mixture frequently during 10 minutes, or until all of the calcium aminosalicylate is dissolved. Add 25 ml. of glacial acetic acid and 20 ml. of potassium bromide solution (1 in 4), and proceed as directed in the *Assay* under *Calcium Aminosalicylate*, page 113, beginning with "Cool to 15°. . . ." Each ml. of 0.1 *M* sodium nitrite is equivalent to 19.92 mg. of $C_{14}H_{12}CaN_2O_6.3H_2O$.

Packaging and storage—Preserve Calcium Aminosalicylate Tablets in tight, light-resistant containers.

Tablets available—Calcium Aminosalicylate Tablets usually available contain the following amounts of calcium aminosalicylate: 500, 580, and 690 mg.

CATEGORY and DOSE—See Calcium Aminosalicylate.

Calcium Benzoylpas



Calcium 4-Benzamidosalicylate

$C_{28}H_{20}CaN_2O_8.5H_2O$ Mol. wt. 642.64

Calcium Benzoylpas contains not less than 98.0 percent and not more than 101.5 percent of $C_{28}H_{20}CaN_2O_8$, calculated on the anhydrous basis.

Description—Calcium Benzoylpas occurs as a white to cream-colored, odorless powder.

Solubility—Calcium Benzoylpas is slightly soluble in water and in methanol. It is very slightly soluble in alcohol, and is practically insoluble in chloroform and in ether.

Identification—

A: Suspend about 1 g. of Calcium Benzoylpas in 20 ml. of 2 *N* acetic acid, shake vigorously for 5 minutes, and filter: the filtrate responds to the tests for *Calcium*, page 808.

B: Dissolve about 100 mg. of Calcium Benzoylpas in 5 ml. of methanol, and add 5 ml. of diluted acetic acid in small portions while mixing. Collect the precipitate on a sintered-glass filter, wash with six 5-ml. portions of water, and dry at 105° for 1 hour: the 4-benzamidosalicylic acid so obtained melts between 243° and 246°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Calcium Benzoylpas, previously dried to constant weight over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Calcium Benzoylpas Reference Standard, similarly measured.

Ultraviolet absorption, page 866—Transfer about 100 mg. of Calcium Benzoylpas, accurately weighed, to a 200-ml. volumetric flask, dissolve in 20 ml. of methanol, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 250-ml. volumetric flask, add 25 ml. of pH 6.0 phosphate buffer, dilute to volume with water, and mix: the ultraviolet absorption spectrum of this solution exhibits maxima and minima at the same wavelengths as that of NF Calcium Benzoylpas Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorption at about 274 mμ, do not differ by more than 2 percent.

Water, page 900—Determine the water content of Calcium Benzoylpas by the titrimetric method: not less than 13 percent and not more than 15 percent of water is found.

Chloride, page 784—Dissolve 500 mg. of Calcium Benzoylpas in 40 ml. of acetone, add 4 ml. of diluted nitric acid, and mix. Add 1 ml. of silver nitrate T.S. in sufficient water to make 50 ml., and mix: this solution shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (0.014 percent).

Heavy metals, *Method II,* page 806—The heavy metals limit for Calcium Benzoylpas is 30 parts per million.

3′-Hydroxybenzamide, *m*-aminophenol, and 4-aminosalicylic acid—Transfer 2.00 g. of Calcium Benzoylpas to a 40-ml. centrifuge tube, add 10.0 ml. of methanol, and shake for 1 minute. Add 10.0 ml. of 2 *N* acetic acid, shake for 15 minutes, and centrifuge until a clear supernatant layer is obtained. Spot 10 µl. of the clear liquid on a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture. Apply to the same plate 5-µl. portions of separate methanol control solutions containing, respectively, in each ml., 200.0 mcg. of 3′-hydroxybenzamide, 100.0 mcg. of *m*-aminophenol, and 400.0 mcg. of 4-aminosalicylic acid. Also, apply to the same plate 5 µl. of a combined control solution in methanol containing in each ml. 200.0 mcg. of 3′-hydroxybenzamide, 100.0 mcg. of *m*-aminophenol, 400.0 mcg. of 4-aminosalicylic acid, and 1.0 mg. of NF Calcium Benzoylpas Reference Standard. Allow the spots to dry, and develop the chromatogram in *n*-butanol saturated with stronger ammonia water (prepared as follows: mix 200 ml. of *n*-butanol with 150 ml. of stronger ammonia water, shake carefully, let stand for at least 12 hours, and discard the aqueous layer) until the solvent front has moved at least 12 cm. from the origin. Remove the plate from the developing chamber, and allow the solvent to evaporate. Locate the spots on the plate by exposing to shortwave ultraviolet light, then spraying with a 1 in 100 solution of 2,6-dichloroquinone-chlorimide in alcohol, and finally expose the plate to fumes of stronger ammonia water for a few minutes: any spots from the sample solution are not greater in size or intensity than the spots, occurring at the respective R_f values, produced by the control solutions of 3′-hydroxybenzamide (0.1 percent), *m*-aminophenol (0.05 percent), and 4-aminosalicylic acid (0.2 percent).

Assay—Transfer about 400 mg. of Calcium Benzoylpas, accurately weighed, to a 200-ml. volumetric flask, dissolve in 40 ml. of anhydrous methanol, immediately add 30 ml. of water, and with constant swirling add 30.0 ml. of 0.1 *N* silver nitrate. Shake well, dilute to volume with water, and mix. When the precipitate has coagulated, filter, avoiding evaporation of the filtrate. To 100.0 ml. of the clear filtrate add 3 ml. of nitric acid and 5 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 0.1 *N* silver nitrate is equivalent to 27.63 mg. of $C_{28}H_{20}CaN_2O_8$.

Packaging and storage—Preserve Calcium Benzoylpas in tight, light-resistant containers.

CATEGORY—Antibacterial (tuberculostatic).

USUAL DOSE RANGE—**10** to **15 g.** daily in two or three divided doses.

Calcium Benzoylpas Tablets

Calcium Benzoylpas Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{28}H_{20}CaN_2O_8 . 5H_2O$.

Identification—

A: Suspend a quantity of powdered Calcium Benzoylpas Tablets, equivalent to about 1 g. of calcium benzoylpas, in 20 ml. of 2 *N* acetic acid, shake vigorously for 5 minutes, and filter: the clear filtrate responds to the tests for *Calcium,* page 808.

B: The ultraviolet absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of the Reference Standard solution, prepared as directed in the *Assay.*

Disintegration, page 878—The disintegration time limit for Calcium Benzoylpas Tablets is 30 minutes.

Weight variation, page 901—Calcium Benzoylpas Tablets meet the requirements of the weight variation test for tablets.

3′-Hydroxybenzamide, *m*-aminophenol, and 4-aminosalicylic acid—Weigh accurately a quantity of finely powdered Calcium Benzoylpas Tablets, equivalent to 2.0 g. of calcium benzoylpas, and transfer to a 40-ml. centrifuge tube. Proceed as directed in the test for *3′-Hydroxybenzamide, m-aminophenol, and 4-aminosalicylic acid* under *Calcium Benzoylpas,* page 116, beginning with ". . . add 10 ml. of methanol, and shake for 1 minute," except use 10-µl. portions, rather than 5-µl. portions, of each control solution: any spots from the sample solution are not greater in size or intensity than the spots, occurring at the respective R_f values, produced by the control solutions of 3′-hydroxybenzamide (0.2 percent), *m*-aminophenol (0.1 percent), and 4-aminosalicylic acid (0.4 percent).

Assay—Weigh and finely powder not less than 20 Calcium Benzoylpas Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 80 mg. of calcium benzoylpas, to a 200-ml. volumetric flask, add 20 ml. of methanol, shake to disperse the powder, dilute to volume with water, and mix. Filter, discarding the first 20 ml. of filtrate. Transfer 5.0 ml. of the subsequent clear filtrate to a 250-ml. volumetric flask, add 25 ml. of pH 6.0 phosphate buffer, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Calcium Benzoylpas Reference Standard, in the same medium, at a concentration of about 8 mcg. per ml., in 1-cm. cells, at the maximum at about 274 mμ, with a suitable spectrophotometer, using as the blank a solution consisting of 25 ml. of pH 6.0 phosphate buffer, 5 ml. of methanol, and 220 ml. of water. Calculate the quantity, in mg., of $C_{28}H_{20}CaN_2O_8 . 5H_2O$ in the portion of Tablets taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Calcium Benzoylpas Tablets in well-closed, light-resistant containers.

Tablets available—Calcium Benzoylpas Tablets usually available contain the following amount of calcium benzoylpas: 500 mg.

Category and Dose—See Calcium Benzoylpas.

Calcium Carbonate Tablets

Calcium Carbonate Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $CaCO_3$.

Identification—The addition of acetic acid to Calcium Carbonate Tablets produces effervescence, and the resulting solution, after being boiled to expel carbon dioxide and neutralized with ammonia T.S., responds to the tests for *Calcium*, page 808.

Barium or strontium—Powder several Calcium Carbonate Tablets, mix a portion of the powder, equivalent to about 2 g. of calcium carbonate, with 100 ml. of water, and add hydrochloric acid dropwise, with agitation, until no more effervescence takes place: this solution does not impart a yellowish green or red color to a nonluminous flame.

Disintegration, page 878—The disintegration time limit for Calcium Carbonate Tablets, using simulated gastric fluid T.S. as the test medium in place of water, is 30 minutes.

Weight variation, page 901—Calcium Carbonate Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Calcium Carbonate Tablets. Weigh accurately a portion of the powder, equivalent to about 200 mg. of calcium carbonate, transfer to a suitable crucible, and ignite to constant weight. Cool the crucible, add 10 ml. of water, and dissolve the residue by adding sufficient diluted hydrochloric acid, dropwise, to achieve complete solution. Transfer the solution completely to a suitable container, dilute to 150 ml. with water, add 15 ml. of sodium hydroxide T.S., and 300 mg. of hydroxy naphthol blue, and titrate with 0.05 *M* disodium ethylenediaminetetraacetate until the solution is deep blue in color. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 5.004 mg. of $CaCO_3$.

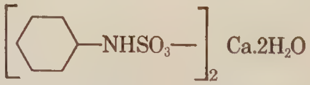
Packaging and storage—Preserve Calcium Carbonate Tablets in well-closed containers.

Tablets available—Calcium Carbonate Tablets usually available contain the following amounts of calcium carbonate: 600 mg. and 1 g.

Category—Antacid.

Usual dose of calcium carbonate—**1** to **2 g.** between meals.

Calcium Cyclamate



Calcium Cyclohexanesulfamate

$C_{12}H_{24}CaN_2O_6S_2 . 2H_2O$ Mol. wt. 432.57

Calcium Cyclamate contains not less than 98.0 percent and not more than 101.0 percent of $C_{12}H_{24}CaN_2O_6S_2$, calculated on the anhydrous basis.

Description—Calcium Cyclamate occurs as white crystals or as a white, crystalline powder. It is odorless. Calcium Cyclamate in dilute solution is about 30 times as sweet as sucrose. Its solutions are neutral to litmus.

Solubility—Calcium Cyclamate is freely soluble in water and in propylene glycol. It is sparingly soluble in alcohol, and is practically insoluble in chloroform and in ether.

Identification—

A: To 10 ml. of a solution of Calcium Cyclamate (1 in 100) add 1 ml. of hydrochloric acid, then add 1 ml. of barium chloride T.S.: the solution remains clear. Add 1 ml. of sodium nitrite solution (1 in 10): a white precipitate is formed.

B: A 1 in 100 solution of Calcium Cyclamate responds to the tests for *Calcium*, page 808.

Water, page 900—Determine the water content of Calcium Cyclamate by the titrimetric method: not less than 6 percent and not more than 9 percent is found.

Arsenic—A *Test Preparation* prepared with 3.33 g. of Calcium Cyclamate, as directed for organic compounds, meets the requirements of the *Arsenic Test*, page 777 (3 parts per million As).

Selenium—A *Test Preparation* prepared with 200 mg. of Calcium Cyclamate meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Heavy metals, page 806—Dissolve 1 g. of Calcium Cyclamate in 25 ml. of water: the heavy metals limit for Calcium Cyclamate is 10 parts per million.

Cyclohexylamine—

Alkaline disodium edetate solution—Mix 100 g. of disodium edetate with 400 ml. of water, add 340 ml. of sodium hydroxide solution (1 in 10), dilute to 1000 ml. with water, and mix to dissolve.

Methyl orange-boric acid solution—Dissolve 200 mg. of methyl orange and 3.5 g. of boric acid in 100 ml. of water, heating on a steam bath to effect solution. Allow to stand for at least 24 hours, and filter before use.

Standard preparation—Transfer 100.0 mg. of cyclohexylamine to a 100-ml. volumetric flask, dissolve in a mixture of 50 ml. of water and 0.5 ml. of hydrochloric acid, dilute to volume with water, and mix. Transfer 5.0 ml. of the solution to a second 100-ml. volumetric flask, dilute to volume with water, and mix. Transfer 5.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with water, and mix.

Test preparation—Transfer 10.0 g. of Calcium Cyclamate to a 100-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix.

Procedure—Transfer 10.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 50-ml. glass-stoppered centrifuge tubes, and transfer 10.0 ml. of water to a third tube to serve as a blank. To each tube add 3.0 ml. of *Alkaline disodium edetate solution* and 15.0 ml. of a 20:1 mixture of chloroform and *n*-butanol, shake the tubes for 2 minutes, and centrifuge. Remove and discard the aqueous layer in each tube, and then transfer 10.0 ml. of the chloroform solution from each tube to separate centrifuge tubes. To each tube add 2.0 ml. of *Methyl orange-boric acid solution,* shake the tubes for 2 minutes, and centrifuge. Remove and discard the aqueous layer in each tube, then add to each tube 1 g. of anhydrous sodium sulfate, shake well, and allow to settle. Transfer 5.0 ml. of each clear chloroform solution into separate test tubes, add 0.5 ml. of a 50:1 mixture of methanol and sulfuric acid, and mix. Concomitantly determine the absorbance of the solutions, in 1-cm. cells, at the maximum at about 520 mμ, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance of the solution from the *Test preparation* does not exceed that from the *Standard preparation,* corresponding to not more than 25 parts per million of cyclohexylamine.

Dicyclohexylamine—

Alkaline disodium edetate solution—Prepare as directed under *Cyclohexylamine.*

Reagent solution A—To about 60 ml. of water add 75 mg. of bromophenol blue followed by 10 ml. of 0.1 *M* sodium bicarbonate, and stir without heating until solution is complete. Adjust the pH to 4.0 with 0.2 *N* hydrochloric acid, dilute to 100 ml. with water, and mix. Store in a cool, dark place and do not use after 48 hours.

Reagent solution B—Mix 200 ml. of 1 *N* hydrochloric acid with 166 ml. of glacial acetic acid, dilute to 1000 ml. with water, and mix.

Procedure—Transfer 10.0 g. of Calcium Cyclamate to a separator, dissolve in 100 ml. of *Alkaline disodium edetate solution,* and extract with one 10-ml. portion and two 5-ml. portions of chloroform, combining the extracts in a second separator. To the second separator add 100 ml. of water, 3.0 ml. of *Reagent solution B*, and 1.0 ml. of *Reagent solution A*, then shake the mixture for 3 minutes, and allow to stand for 30 minutes protected from direct sunlight. Quantitatively transfer the chloroform layer to a 25-ml. volumetric flask, dilute to volume with chloroform, and mix. Determine the absorbance of this solution in a

5-cm. cell, at the maximum at about 410 mμ, with a suitable spectrophotometer, using chloroform as the blank. Concomitantly determine the absorbance of a reagent blank prepared with the same quantities of the same reagents, omitting only the test sample: the difference between the absorbance of the solution from the sample and that of the reagent blank is not greater than 0.075, indicating no measurable quantity of dicyclohexylamine in the sample.

Assay—Transfer about 400 mg. of Calcium Cyclamate, accurately weighed, to a 250-ml. beaker, and dissolve in a mixture of 50 ml. of water and 5 ml. of hydrochloric acid. Titrate at room temperature with 0.1 *M* sodium nitrite. Add the last 1 ml. of titrant dropwise until a blue color is produced immediately when a glass rod dipped into the titrated solution is spotted on starch iodide paper. When the titration is complete, the endpoint is reproducible after the solution has been allowed to stand for 1 minute. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 19.83 mg. of $C_{12}H_{24}CaN_2O_6S_2$.

Packaging and storage—Preserve Calcium Cyclamate in well-closed containers.

CATEGORY—Non-nutritive sweetener.

Calcium Cyclamate and Calcium Saccharin Solution[*]

Calcium Cyclamate and Calcium Saccharin Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_{12}H_{24}CaN_2O_6S_2.2H_2O$ (calcium cyclamate) and of $C_{14}H_8CaN_2O_6S_2.3^1/_2H_2O$ (calcium saccharin). The labeled concentration of calcium cyclamate is not less than 6.0 percent and is at least 10 times the labeled concentration of calcium saccharin.

Description—Calcium Cyclamate and Calcium Saccharin Solution is a clear, colorless liquid having a sweet taste.

Identification—

A: Dilute 1 ml. of Calcium Cyclamate and Calcium Saccharin Solution with water to 10 ml., acidify with hydrochloric acid, and add 1 ml. of barium chloride T.S.: the solution remains clear. Add 1 ml. of sodium nitrite solution (1 in 10): a white precipitate is formed.

B: The solution employed for measurement of absorbance in the *Assay for calcium saccharin* exhibits an absorbance maximum at 266 ± 2 mμ, and a minimum at 247 ± 2 mμ.

C: Calcium Cyclamate and Calcium Saccharin Solution responds to the tests for *Calcium*, page 808.

Assay for calcium cyclamate—Transfer an accurately measured volume of Calcium Cyclamate and Calcium Saccharin Solution, equivalent to about 500 mg. of calcium cyclamate, to a 250-ml. beaker, and add about 50 ml. of water and 5 ml. of hydrochloric acid. Proceed as directed in the *Assay* under *Calcium Cyclamate*, page 118, beginning with "Titrate at room temperature. . . ." Each ml. of 0.1 *M* sodium nitrite is equivalent to 21.63 mg. of $C_{12}H_{24}CaN_2O_6S_2.2H_2O$.

Assay for calcium saccharin—Transfer an accurately measured volume of Calcium Cyclamate and Calcium Saccharin Solution, equivalent to about 150 mg. of calcium saccharin, to a 250-ml. separator, and wash with three 50-ml. portions of chloroform, discarding the chloroform layer after each extraction. Filter the aqueous layer after each extraction. Filter the aqueous layer through paper previously moistened with water, into a 100-ml. volumetric flask. Add the water rinsings of the separator and the filter to the flask, add water to volume, and mix. Pipet 5.0 ml. of the solution into another 100-ml. volumetric flask, add water to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Saccharin Reference Standard, in the same medium, at a concentration of about 60 mcg. per ml. in 1-cm. cells, at the maximum at about 266 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{14}H_8CaN_2O_6S_2.3^1/_2H_2O$ in each ml. of the Solution taken by the formula $2 \times (C/V) \times 1.276\,(A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., V is the volume, in ml., of the Solution taken, A_U is the absorbance of the sample solution, A_S is the absorbance of the Reference Standard solution, and 1.276 is the conversion factor relating calcium saccharin to saccharin.

Packaging and storage—Preserve Calcium Cyclamate and Calcium Saccharin Solution in tight containers.

Solution available—Calcium Cyclamate and Calcium Saccharin solution usually available contains 6 percent of calcium cyclamate and 0.6 percent of calcium saccharin.

CATEGORY—See Calcium Cyclamate.

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[*] Patented. See notice, page ii.

Calcium Cyclamate and Calcium Saccharin Tablets*

Calcium Cyclamate and Calcium Saccharin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_{12}H_{24}CaN_2O_6S_2 \cdot 2H_2O$ (calcium cyclamate) and of $C_{14}H_8CaN_2O_6S_2 \cdot 3^1/_2H_2O$ (calcium saccharin). The labeled content of calcium cyclamate is at least 10 times the labeled content of calcium saccharin.

Identification—

A: Dissolve 4 Calcium Cyclamate and Calcium Saccharin Tablets in 20 ml. of water: the solution responds to *Identification tests A* and *C* under *Calcium Cyclamate and Calcium Saccharin Solution*, page 120.

B: The ultraviolet absorption spectrum of the solution employed for measurement of absorbance in the *Assay for calcium saccharin* exhibits a maximum at 266 ± 2 mμ, and a minimum at 247 ± 2 mμ.

Solution—Place 5 Calcium Cyclamate and Calcium Saccharin Tablets in a 250-ml. beaker containing 150 ml. of water at 25°. Stir the solution for 5 minutes: all of the tablets dissolve.

Weight variation, page 901—Calcium Cyclamate and Calcium Saccharin Tablets meet the requirements of the weight variation test for tablets.

Assay for calcium cyclamate—Weigh and finely powder not less than 20 Calcium Cyclamate and Calcium Saccharin Tablets. Weigh accurately a portion of the powder, equivalent to about 400 mg. of calcium cyclamate, transfer to a 250-ml. beaker, and dissolve in a mixture of 50 ml. of water and 5 ml. of hydrochloric acid. Proceed as directed in the *Assay* under *Calcium Cyclamate*, page 118, beginning with "Titrate at room temperature. . . ." Each ml. of 0.1 *M* sodium nitrite is equivalent to 21.63 mg. of $C_{12}H_{24}CaN_2O_6S_2 \cdot 2H_2O$.

Assay for calcium saccharin—Weigh accurately a portion of the powdered Calcium Cyclamate and Calcium Saccharin Tablets prepared for the *Assay for calcium cyclamate*, equivalent to about 10 mg. of calcium saccharin, transfer to a 100-ml. volumetric flask, add water to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Saccharin Reference Standard, in the same medium, at a concentration of about 100 mcg. per ml. in 1-cm. cells, at the maximum at about 266 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{14}H_8CaN_2O_6S_2 \cdot 3^1/_2H_2O$ in the portion of the Tablets taken by the formula $0.1C \times 1.276 (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, A_S is the absorbance of the Reference Standard solution, and 1.276 is the conversion factor relating calcium saccharin to saccharin.

Packaging and storage—Preserve Calcium Cyclamate and Calcium Saccharin Tablets in tight containers.

Tablets available—Calcium Cyclamate and Calcium Saccharin Tablets usually available contain the following: 50 mg. of calcium cyclamate and 5 mg. of calcium saccharin.

CATEGORY—See Calcium Cyclamate.

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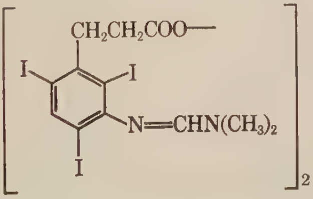
* Patented. See notice, page ii.

Calcium Ipodate



Calcium 3-[[(Dimethylamino)methylene]amino]-2,4,6-triiodohydrocinnamate

$C_{24}H_{24}CaI_6N_4O_4$ Mol. wt. 1233.99

Calcium Ipodate contains not less than 97.5 percent and not more than 102.5 percent of $C_{24}H_{24}CaI_6N_4O_4$, calculated on the anhydrous basis.

Description—Calcium Ipodate occurs as a white to off-white, odorless, fine crystalline powder.

Solubility—Calcium Ipodate is slightly soluble in water, in alcohol, in chloroform, and in methanol.

Identification—

A: Heat about 500 mg. of Calcium Ipodate in a porcelain crucible over a free flame: violet vapors of iodine are evolved.

B: Dissolve about 200 mg. of Calcium Ipodate in 10 ml. of acetic acid, and add 2 ml. of ammonium oxalate T.S.: a white precipitate, which is soluble in diluted hydrochloric acid, is produced.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Calcium Ipodate, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Calcium Ipodate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Calcium Ipodate in methanol exhibits maxima and minima at the same wavelengths as that of NF Calcium Ipodate Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorption occurring at about 235 mμ, do not differ by more than 3 percent.

Water, page 900—Determine the water content of Calcium Ipodate by the titrimetric method: not more than 3.5 percent is found.

Iodide or iodine—Dissolve about 200 mg. of Calcium Ipodate in 10 ml. of acetic acid, add 1 ml. of chloroform, and shake vigorously. Allow the layers to separate: the chloroform layer shows no violet color (absence of free iodine). Add 1 ml. of 0.1 *N* potassium iodate, shake vigorously, and allow the layers to separate: the chloroform layer shows at most a slight trace of violet color.

Heavy metals, *Method II*, page 806—The heavy metals limit for Calcium Ipodate is 30 parts per million.

Assay—Transfer about 300 mg. of Calcium Ipodate, accurately weighed, to a 250-ml. glass-stoppered flask, add 30 ml. of sodium hydroxide solution (1 in 20) and 500 mg. of powdered zinc, and reflux the mixture for 60 minutes. Cool, wash the condenser with 20 ml. of water, and filter the mixture. Wash the flask and filter with small portions of water, adding the washings to the filtrate. Add to the filtrate 5 ml. of glacial acetic acid and 3 drops of eosin Y T.S., and titrate with 0.05 *N* silver nitrate until the entire mixture changes to a permanent pink color. Each ml. of 0.05 *N* silver nitrate is equivalent to 10.28 mg. of $C_{24}H_{24}CaI_6N_4O_4$.

Packaging and storage—Preserve Calcium Ipodate in tight containers.

CATEGORY—Diagnostic aid (radiopaque—cholangiography and cholecystography).

USUAL DOSE—**3** to **6 g.,** as a single dose given 10 to 12 hours before the examination.

Calcium Ipodate for Oral Suspension

Calcium Ipodate for Oral Suspension is a dry mixture of calcium ipodate and one or more suitable suspending, dispersing, and flavoring agents. It contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{24}CaI_6N_4O_4$.

Identification—Stir an amount of Calcium Ipodate for Oral Suspension, equivalent to about 2 g. of calcium ipodate, with 100 ml. of water for several minutes, and filter the suspension with the aid of suction. Wash the filter with several small portions of water, and dry the residue in vacuum at 60° for 4 hours: the calcium ipodate so obtained responds to the *Identification tests* under *Calcium Ipodate*, page 121.

Assay—Weigh accurately the contents of not less than 10 containers of Calcium Ipodate for Oral Suspension, and mix well. Transfer an accurately weighed portion of the granules, equivalent to about 300 mg. of calcium ipodate, to a 250-ml. glass-stoppered flask, and continue as directed in the *Assay* under *Calcium Ipodate*, page 121, beginning with " . . . add 30 ml. of sodium hydroxide solution (1 in 20). . . . "

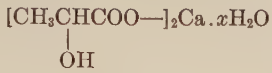
Weight variation, page 901—Calcium Ipodate for Oral Suspension meets the requirements of the weight variation test for powders.

Packaging and storage—Preserve Calcium Ipodate for Oral Suspension in well-closed containers.

Size available—Calcium Ipodate for Oral Suspension usually available contains the following amount of calcium ipodate: 3 g.

CATEGORY and DOSE—See Calcium Ipodate.

Calcium Lactate



$$[\mathrm{CH_3\underset{\underset{OH}{|}}{C}HCOO—}]_2\mathrm{Ca}.x\mathrm{H_2O}$$

$C_6H_{10}CaO_6.xH_2O$ Mol. wt. (anhydrous) 218.22

Calcium Lactate contains not less than 98.0 percent and not more than 101.0 percent of $C_6H_{10}CaO_6$, calculated on the dried basis.

Description—Calcium Lactate occurs as white, almost odorless, granules or powder. The pentahydrate is somewhat efflorescent and at 120° becomes anhydrous.

Solubility—Calcium Lactate pentahydrate is soluble in water. It is practically insoluble in alcohol.

Identification—A solution of Calcium Lactate (1 in 20) responds to the tests for *Calcium*, page 808, and for *Lactate*, page 809.

Loss on drying, page 814—Distribute a 1-g. to 2-g. sample of Calcium Lactate evenly in a suitable weighing dish to a depth not exceeding 3 mm., and dry at 120° for 4 hours: the pentahydrate loses not less than 24 percent and not more than 30 percent of its weight; the trihydrate loses not less than 15 percent and not more than 20 percent of its weight; the monohydrate loses not less than 5 percent and not more than 8 percent of its weight; and the dried form loses not more than 3 percent of its weight.

Acidity—Titrate 20 ml. of a solution of Calcium Lactate (1 in 20) with 0.1 *N* sodium hydroxide, using phenolphthalein T.S. as the indicator: not more than 0.5 ml. is required for neutralization (0.45 percent as lactic acid).

Heavy metals, page 806—Dissolve 1 g. of Calcium Lactate in 2.5 ml. of diluted acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Calcium Lactate is 20 parts per million.

Magnesium and alkali salts—Mix 1 g. of Calcium Lactate with 40 ml. of water, carefully add 1 ml. of hydrochloric acid, heat the solution to boiling, and add rapidly 40 ml. of oxalic acid T.S. Add immediately to the warm mixture 2 drops of methyl red T.S., and then ammonia T.S., dropwise, from a buret, until the mixture is just alkaline. Cool to room temperature, transfer to a 100-ml. graduated cylinder, dilute to 100 ml. with water, mix, and let stand for 4 hours or overnight. Filter, and transfer 50 ml. of the clear filtrate, to which has been added 0.5 ml. of sulfuric acid, to a tared platinum dish. Evaporate the mixture on a steam bath to a small volume. Carefully heat over a free flame to dryness, and continue heating to complete decomposition and volatilization of ammonium salts. Finally ignite the residue to constant weight. The weight of the residue does not exceed 5 mg. (1 percent).

Volatile fatty acid—Stir about 500 mg. of Calcium Lactate with 1 ml. of sulfuric acid, and warm: the mixture does not emit an odor of volatile fatty acid.

Assay—Weigh accurately an amount of Calcium Lactate, equivalent to about 350 mg. of $C_6H_{10}CaO_6$, transfer to a suitable container, and dissolve it in 150 ml. of water containing 2 ml. of diluted hydrochloric acid. While stirring, preferably with a magnetic stirrer, add about 30 ml. of 0.05 *M* disodium ethylenediaminetetraacetate from a 50-ml. buret, then add 15 ml. of sodium hydroxide T.S. and 300 mg. of hydroxy naphthol blue indicator, and continue the titration to a blue end-point. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 10.91 mg. of $C_6H_{10}CaO_6$.

Labeling—The label shall declare the degree of hydration of Calcium Lactate or whether it is the dried form. When the quantity of Calcium Lactate is indicated in the labeling of any preparation containing Calcium Lactate, this shall be understood to be in terms of Calcium Lactate pentahydrate ($C_6H_{10}CaO_6.5H_2O$).

Packaging and storage—Preserve Calcium Lactate in tight containers.

CATEGORY—Calcium supplement.

USUAL DOSE RANGE—**1** to **5 g.** three times a day.

Calcium Lactate Tablets

Calcium Lactate Tablets contain not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_6H_{10}CaO_6.5H_2O$.

NOTE: An equivalent amount of calcium lactate with less water of hydration may be used in place of $C_6H_{10}CaO_6.5H_2O$ in preparing Calcium Lactate Tablets.

Identification—A filtered solution of Calcium Lactate Tablets, equivalent to calcium lactate solution (1 in 20), responds to the tests for *Calcium*, page 808, and for *Lactate*, page 809.

Disintegration, page 878—The disintegration time limit for Calcium Lactate Tablets is 30 minutes.

Weight variation, page 901—Calcium Lactate Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Calcium Lactate Tablets. Weigh accurately a portion of the powder, equivalent to about 350 mg. of $C_6H_{10}CaO_6$, transfer to a suitable crucible, and ignite, gently at first, until free from carbon. Cool the crucible, add 10 ml. of water, and dissolve the residue by adding sufficient diluted hydrochloric acid, dropwise, to achieve complete solution. Transfer the solution completely to a suitable container, and dilute to 150 ml. While stirring, preferably with magnetic stirrer, add about 30 ml. of 0.05 *M* disodium ethylenediaminetetraacetate from a 50-ml. buret, then add 15 ml. of sodium hydroxide T.S. and 300 mg. of hydroxy naphthol blue indicator, and continue the titration to a blue endpoint. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 15.42 mg. of $C_6H_{10}CaO_6 . 5H_2O$.

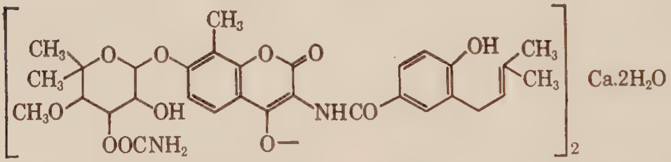
Labeling—The quantity of calcium lactate in the labeling of Calcium Lactate Tablets shall be in terms of calcium lactate pentahydrate.

Packaging and storage—Preserve Calcium Lactate Tablets in tight containers.

Tablets available—Calcium Lactate Tablets usually available contain the following amounts of calcium lactate (pentahydrate): 300 and 600 mg.

CATEGORY and DOSE—See Calcium Lactate.

Calcium Novobiocin



$C_{62}H_{70}CaN_4O_{22} . 2H_2O$ Mol. wt. 1299.37

Calcium Novobiocin contains the equivalent of not less than 80.0 percent of novobiocin (as the free acid, $C_{31}H_{36}N_2O_{11}$), calculated on the dried basis. Calcium Novobiocin conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Calcium Novobiocin is a white or practically white, crystalline powder. It is odorless or practically odorless.

Solubility—Calcium Novobiocin is slightly soluble in water and in ether. It is sparingly soluble in alcohol, and is very slightly soluble in chloroform.

Packaging and storage—Preserve Calcium Novobiocin in tight containers.

CATEGORY—Antibacterial.

USUAL DOSE—The equivalent of **250 mg.** of novobiocin acid every 6 hours.

USUAL DOSE RANGE—**250** to **500 mg.** of novobiocin acid.

Calcium Novobiocin Oral Suspension

Calcium Novobiocin Oral Suspension is a suspension of calcium novobiocin in an aqueous vehicle, containing one or more suitable suspending agents, colors, flavors, and preservatives. It contains, in each 100 ml., an amount of calcium novobiocin equivalent to not less than 2.25 g. and not more than 3.00 g. of novobiocin (as the free acid, $C_{31}H_{36}N_2O_{11}$). Calcium Novobiocin Oral Suspension conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Calcium Novobiocin Oral Suspension in tight containers, protected from light.

CATEGORY and DOSE—See Calcium Novobiocin.

Calcium Oxytetracycline

$C_{44}H_{46}CaN_4O_{18}$ Mol. wt. 958.95

Calcium Oxytetracycline has a potency of not less than 865 mcg. of oxytetracycline per mg., calculated on the anhydrous basis. Calcium Oxytetracycline conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Calcium Oxytetracycline is a yellow to light brown, crystalline powder. The pH of a 1 in 40 suspension is about 7.0.

Solubility—Calcium Oxytetracycline is insoluble in water.

Packaging and storage—Preserve Calcium Oxytetracycline in tight, light-resistant containers in a cool place.

CATEGORY—Antibacterial.

USUAL DOSE—**250 mg.** four times a day.

USUAL DOSE RANGE—**250 to 500 mg.**

Calcium Oxytetracycline Oral Suspension*

Calcium Oxytetracycline Oral Suspension is a suspension of calcium oxytetracycline in an aqueous vehicle containing one or more suitable suspending agents, flavors, colors, and preservatives. It contains the equivalent of not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{22}H_{24}N_2O_9$ (anhydrous oxytetracycline). Calcium Oxytetracycline Oral Suspension conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Calcium Oxytetracycline Oral Suspension in tight, light-resistant containers in a cool place.

Suspension available—Calcium Oxytetracycline Oral Suspension usually available contains an amount of calcium oxytetracycline equivalent to 125 mg. of oxytetracycline in each 5 ml.

CATEGORY and DOSE—See Calcium Oxytetracycline.

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* Patented. See notice, page ii.

Dibasic Calcium Phosphate

$CaHPO_4$ Mol. wt. (anhydrous) 136.06

Dibasic Calcium Phosphate is anhydrous or contains two molecules of water of hydration. It contains an amount of calcium pyrophosphate ($Ca_2P_2O_7$) equivalent to not less than 98.0 percent and not more than 100.5 percent of $CaHPO_4$, calculated on the ignited basis.

Description—Dibasic Calcium Phosphate occurs as a white, odorless, tasteless powder and is stable in air.

Solubility—Dibasic Calcium Phosphate is practically insoluble in water, soluble in diluted hydrochloric and nitric acids, and is insoluble in alcohol.

Identification—

A: Dissolve about 100 mg. of Dibasic Calcium Phosphate by warming with a mixture of 5 ml. of diluted hydrochloric acid and 5 ml. of water, add 2.5 ml. of ammonia T.S. dropwise, with shaking, and then add 5 ml. of ammonium oxalate T.S.: a white precipitate is formed.

B: To 10 ml. of a warm solution (1 in 100) of Dibasic Calcium Phosphate in a slight excess of nitric acid add 10 ml.

of ammonium molybdate T.S.: a yellow precipitate of ammonium phosphomolybdate is formed.

Loss on ignition—Weigh accurately about 1 g. of Dibasic Calcium Phosphate and ignite, preferably in a muffle furnace at 800° to 825°, to constant weight: anhydrous Dibasic Calcium Phosphate loses not less than 6.6 percent and not more than 8.5 percent of its weight, and hydrous Dibasic Calcium Phosphate loses not less than 24.5 percent and not more than 26.5 percent of its weight.

Acid-insoluble substances—Heat 5 g. of Dibasic Calcium Phosphate with a mixture of 40 ml. of water and 10 ml. of hydrochloric acid until no more dissolves, and dilute to 100 ml. with water. If an insoluble residue remains, filter, wash with hot water until the last washing does not give a reaction for chloride, and dry the residue at 105° for 1 hour: the weight of the residue does not exceed 5 mg. (0.1 percent).

Carbonate—Mix 1 g. of Dibasic Calcium Phosphate with 5 ml. of water, and add 2 ml. of hydrochloric acid: no effervescence occurs.

Chloride, page 784—To 300 mg. of Dibasic Calcium Phosphate add 10 ml. of water and 2 ml. of nitric acid, and warm gently, if necessary, until no more dissolves. Dilute to 25 ml., filter if necessary, and add 1 ml. of silver nitrate T.S.: the turbidity does not exceed that produced by 1 ml. of 0.02 *N* hydrochloric acid (0.25 percent).

Fluoride—Place 2 g. of Dibasic Calcium Phosphate together with 5 ml. of perchloric acid, 15 ml. of water, and a few glass beads in a 50-ml. distilling flask connected with a condenser. The flask also is equipped with a thermometer and a capillary tube, both of which extend into the liquid. Connect a small dropping funnel, filled with water, to the capillary tube. Support the flask on an asbestos mat with a hole that exposes about one-third of the flask to the flame. Distil until the temperature reaches 135°, receiving the distillate under the surface of a few ml. of water, and then maintain at 135° to 140° by adding water from the funnel. Continue the distillation until 70 ml. has been collected, dilute the distillate to 80 ml. with water, and mix. Place 40 ml. of the solution in a 50-ml. color-comparison tube. In a similar tube place 40 ml. of water as a control. Add to each tube 0.1 ml. of sodium alizarinsulfonate solution (1 in 1000), and mix. Add dropwise, and with stirring, 0.05 *N* sodium hydroxide to the tube containing the distillate until the color just matches that of the control, which is faintly pink. Then add to each tube 1.0 ml. of 0.1 *N* hydrochloric acid, and mix. From a buret, graduated in 0.05-ml. intervals, add slowly to the tube containing the distillate enough thorium nitrate solution, made by dissolving 250 mg. of thorium nitrate in 1000 ml. of water, so that, after mixing, the color of the liquid just changes to a faint pink. Note the volume of thorium nitrate solution added, add exactly the same volume to the control, and mix. Then add sodium fluoride T.S. from a buret to the control to make the colors of the two tubes match after dilution to the same volume. Mix, and allow all air bubbles to escape before making the final color comparison. Check the end-point by adding 1 or 2 drops of sodium fluoride T.S. to the control: a distinct change in color takes place. Not more than 5 ml. of the sodium fluoride T.S. is required (50 parts per million). Each ml. of sodium fluoride T.S. is equivalent to 10 mcg. of fluoride (F).

Sulfate, page 784—Dissolve 1 g. of Dibasic Calcium Phosphate in the smallest possible amount of diluted hydrochloric acid, dilute to 100.0 ml. with water and filter if necessary. To 20 ml. of the filtrate add 1 ml. of barium chloride T.S.: the turbidity does not exceed that produced by 1 ml. of 0.02 *N* sulfuric acid (0.5 percent).

Arsenic—A solution of 1.25 g. of Dibasic Calcium Phosphate in 25 ml. of diluted hydrochloric acid meets the requirements of the *Arsenic Test,* page 777 (8 parts per million As).

Barium—Heat 500 mg. of Dibasic Calcium Phosphate with 10 ml. of water, and add hydrochloric acid dropwise, stirring after each addition, until no more dissolves. Filter, and to the filtrate add 2 ml. of potassium sulfate T.S.: no turbidity is produced within 10 minutes.

Heavy metals, page 806—Warm 1 g. of Dibasic Calcium Phosphate with 3 ml. of diluted hydrochloric acid until no more dissolves, dilute to 50 ml. with water, and filter: the heavy metals limit, determined in 25 ml. of the filtrate, is 30 parts per million.

Assay—Dissolve about 300 mg. of Dibasic Calcium Phosphate, previously ignited at 800° to 825° to constant weight and accurately weighed, in 10 ml. of diluted hydrochloric acid, add about 120 ml. of water and 3 drops of methyl orange T.S., and boil for 30 minutes in a covered container, maintaining the volume of solution constant and acidic during the boiling period by adding diluted hydrochloric acid or water, if necessary. Add 30 ml. of ammonium oxalate T.S. and 2 drops of methyl red T.S., then add dropwise, with constant stirring, a mixture of equal volumes of ammonia T.S. and water until the pink color of the indicator just disappears. Digest on a steam bath for 30 minutes. Cool to room temperature, allow the precipitate to settle, and filter the supernatant liquid through an asbestos mat in a porcelain filter crucible, using gentle suction. Wash the precipitate in the beaker with about 30 ml. of cold (below 20°) wash solution, prepared by diluting 10 ml. of ammonium oxalate T.S. to one liter. Allow the precipitate to settle, and pour the supernatant liquid through the filter. Repeat this washing by decantation three more times. Using the wash solution, transfer the precipitate as completely as possible to the filter. Finally wash the beaker and the filter with two 10-ml. portions of cold (below 20°) water. Place the porcelain filter crucible in the beaker, and add 100 ml. of water and 50 ml. of cold dilute sulfuric acid (1 in 6). Add from a buret 35 ml. of 0.1 *N* potassium permanganate, and stir until the color disappears. Heat to about 70°, and complete the titration with 0.1 *N* potassium permanganate. Each ml. of 0.1 *N* potassium permanganate is equivalent to 6.352 mg. of $CaHPO_4$.

Packaging and storage—Preserve Dibasic Calcium Phosphate in well-closed containers.

Labeling—Label Dibasic Calcium Phosphate to indicate whether it is anhydrous or hydrous.

CATEGORY—Source of Calcium.
USUAL DOSE—**1 g.** three times a day.
USUAL DOSE RANGE—**1** to **5 g.**

Tribasic Calcium Phosphate

Tribasic Calcium Phosphate consists of a variable mixture of calcium phosphates having the approximate composition $10CaO.3P_2O_5.H_2O$. It contains an amount of phosphate (PO_4) equivalent to not less than 90.0 percent of tribasic calcium phosphate, $Ca_3(PO_4)_2$, calculated on the ignited basis.

Description—Tribasic Calcium Phosphate occurs as a white, odorless, and tasteless powder, which is stable in air.

Solubility—Tribasic Calcium Phosphate dissolves readily in diluted hydrochloric and nitric acids. It is insoluble in alcohol and almost insoluble in water.

Identification—

A: To a warm solution of Tribasic Calcium Phosphate in a slight excess of nitric acid, add ammonium molybdate T.S.: a yellow precipitate forms.

B: Dissolve about 100 mg. of Tribasic Calcium Phosphate by warming with 5 ml. of diluted hydrochloric acid and 5 ml. of water, add 1 ml. of ammonia T.S., dropwise, with shaking, and then add 5 ml. of ammonium oxalate T.S.: a white precipitate forms.

C: Tribasic Calcium Phosphate responds to the flame test for *Calcium*, page 808.

Loss on ignition—Ignite Tribasic Calcium Phosphate at about 800° for 30 minutes: it loses not more than 8 percent of its weight.

Water-soluble substances—Digest 2 g. of Tribasic Calcium Phosphate with 100 ml. of water for 30 minutes on a steam bath, cool, add sufficient water to restore the original volume, stir well, and filter. Evaporate to dryness 50 ml. of the filtrate in a tared porcelain dish on a steam bath, and dry the residue at 120° to constant weight: the weight of the residue does not exceed 5 mg. (0.5 percent).

Acid-insoluble substances—If an insoluble residue remains in the test for *Carbonate*, boil the solution, filter, wash the residue well with hot water until the last washing is free from chloride, and ignite the residue to constant weight: the weight of the residue does not exceed 4 mg. (0.2 percent).

Carbonate—Mix 2 g. of Tribasic Calcium Phosphate with 20 ml. of water, and add diluted hydrochloric acid, dropwise, to effect solution: no effervescence occurs when the acid is added.

Chloride, page 784—Dissolve 500 mg. of Tribasic Calcium Phosphate in 25 ml. of diluted nitric acid, and add 1 ml. of silver nitrate T.S.: the turbidity does not exceed that produced by 1 ml. of 0.02 *N* hydrochloric acid (0.14 percent).

Fluoride—Place 2 g. of Tribasic Calcium Phosphate, 5 ml. of perchloric acid, 15 ml. of water, and a few glass beads in a 50-ml. distilling flask connected with a condenser. The flask is also equipped with a thermometer and a capillary tube, both of which must extend into the liquid. Connect a small dropping funnel, filled with water, to the capillary tube. Support the flask on an asbestos mat with a hole which exposes about one-third of the flask to the flame. Distil until the temperature reaches 135°, receiving the distillate under the surface of a few ml. of water; then maintain at 135° to 140° by adding water from the funnel. Continue the distillation until 70 ml. has been collected, dilute the distillate to 80 ml. with water, and mix. Place 40 ml. of the solution in a 50-ml. color-comparison tube. In another similar color-comparison tube place 40 ml. of water as a control. Add to each tube 0.1 ml. of sodium alizarinsulfonate solution (1 in 1000) and mix. Add, dropwise, and with stirring, 0.05 *N* sodium hydroxide to the tube containing the distillate until its color just matches that of the control, which is faintly pink. Then add to each tube 1.0 ml. of 0.1 *N* hydrochloric acid, and mix. From a buret, graduated in 0.05 ml., add slowly to the tube containing the distillate enough thorium nitrate solution, made by dissolving 250 mg. of thorium nitrate in 1000 ml. of water, so that, after mixing, the color of the liquid just changes to a faint pink. Note the volume of thorium nitrate solution added, add exactly the same volume to the control, and mix. Now add to the control sodium fluoride T.S. from a buret to make the colors of the two tubes match after dilution to the same volume. Mix, and allow all air bubbles to escape before making the final color comparison. Check the endpoint by adding 1 or 2 drops of sodium fluoride T.S. to the control: a distinct change in color should take place. Not more than 5 ml. of the sodium fluoride T.S. is required (50 parts per million). Each ml. of sodium fluoride T.S. is equivalent to 10 mcg. of fluoride (F).

Nitrate—Mix 200 mg. of Tribasic Calcium Phosphate with 5 ml. of water, and add just sufficient hydrochloric acid to effect solution. Dilute with water to 10 ml., add 0.1 ml. of indigo carmine T.S., then add, with stirring, 10 ml. of sulfuric acid: the blue color persists for at least 5 minutes.

Sulfate, page 784—Dissolve 500 mg. of Tribasic Calcium Phosphate in the smallest possible amount of diluted hydrochloric acid, dilute to 100 ml. with water, filter, if necessary, and to 25 ml. of the filtrate add 1 ml. of barium chloride T.S.: the turbidity does not exceed that produced by 1 ml. of 0.02 *N* sulfuric acid (0.8 percent).

Arsenic—A solution of 1.25 g. of Tribasic Calcium Phosphate in just sufficient diluted hydrochloric acid to dissolve the sample meets the requirements of the *Arsenic Test,* page 777 (8 parts per million As).

Barium—Mix 500 mg. of Tribasic Calcium Phosphate with 10 ml. of water, heat, and add hydrochloric acid, dropwise, until solution is effected, then add 2 drops of the acid in excess. Filter, and add to the filtrate 1 ml. of potassium sulfate T.S.: no turbidity appears within 15 minutes.

Dibasic salt and calcium oxide—Weigh accurately about 2 g. of Tribasic Calcium Phosphate, and dissolve it by warming with 50.0 ml. of 1 *N* hydrochloric acid. Cool, add 1 or 2 drops of methyl orange T.S., and slowly titrate the excess of 1 *N* hydrochloric acid with 1 *N* sodium hydroxide to a yellow color, vigorously shaking the mixture during titration. Not less than 12.5 ml. and not more than 13.8 ml. of 1 *N* hydrochloric acid is consumed for each g. of salt, calculated on the ignited basis.

Heavy metals, page 806—Mix thoroughly 2 g. of Tribasic Calcium Phosphate with 9 ml. of diluted hydrochloric acid, dilute to 50 ml. with water, and heat to boiling. Cool to room temperature, and filter. Use 25 ml. of the filtrate for the test: the heavy metals limit for Tribasic Calcium Phosphate is 30 parts per million. (NOTE: filter the mixture after the pH adjustment.)

Assay—Weigh accurately about 200 mg. of Tribasic Calcium Phosphate, and dissolve it in a mixture of 25 ml. of water and 10 ml. of diluted nitric acid. Filter, if necessary, wash any precipitate, add sufficient ammonia T.S. to the filtrate to produce a slight precipitate, then dissolve the precipitate by the addition of 1 ml. of diluted nitric acid. Adjust the temperature to about 50°, add 75 ml. of ammonium molybdate T.S., and maintain the temperature at about 50° for 30 minutes, stirring occasionally. Wash the precipitate once or twice with water by decantation, using from 30 to 40 ml. each time. Transfer the precipitate to a filter, and wash with potassium nitrate solution (1 in 100) until the last washing is not acid to litmus paper. Transfer the precipitate and filter to the precipitation vessel with 50 ml. of water, add 40.0 ml. of 1 *N* sodium hydroxide, agitate until the precipitate is dissolved, add 3 drops of phenolphthalein T.S., and then titrate the excess alkali with 1 *N* sulfuric acid. Each ml. of 1 *N* sodium hydroxide is equivalent to 6.743 mg. of $Ca_3(PO_4)_2$.

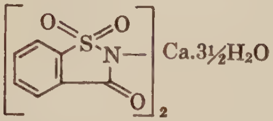
Packaging and storage—Preserve Tribasic Calcium Phosphate in well-closed containers.

CATEGORY—Calcium supplement.

USUAL DOSE RANGE—**1** to **5 g.** three times a day.

Calcium Saccharin and Calcium Cyclamate Solution, page 120
Calcium Saccharin and Calcium Cyclamate Tablets, page 121

Calcium Saccharin



1,2-Benzisothiazolin-3-one 1,1-Dioxide Calcium Salt

$C_{14}H_8CaN_2O_6S_2 . 3^1/_2H_2O$ Mol. wt. 467.49

Calcium Saccharin contains not less than 95.0 percent and not more than 100.5 percent of $C_{14}H_8CaN_2O_6S_2$, calculated on the anhydrous basis.

Description—Calcium Saccharin occurs as white crystals or as a white, crystalline powder. It is odorless or has a faint, aromatic odor, and has an intensely sweet taste even in dilute solutions. Calcium Saccharin in dilute solution is about 300 times as sweet as sucrose.

Solubility—Calcium Saccharin is freely soluble in water.

Identification—

A: Dissolve about 100 mg. of Calcium Saccharin in 5 ml. of sodium hydroxide solution (1 in 20), evaporate the solution to dryness, and gently fuse the residue over a small flame until it no longer evolves ammonia. Allow the residue to cool, dissolve it in 20 ml. of water, neutralize the solution with diluted hydrochloric acid, and filter: the addition of a drop of ferric chloride T.S. to the filtrate produces a violet color.

B: Mix 20 mg. of Calcium Saccharin with 40 mg. of resorcinol, add 10 drops of sulfuric acid, and heat the mixture in a suitable liquid bath at 200° for 3 minutes. Allow it to cool, and add 10 ml. of water and an excess of sodium hydroxide T.S.: a fluorescent green liquid results.

C: A solution of Calcium Saccharin (1 in 10) responds to the tests for *Calcium,* page 808.

D: To 10 ml. of a solution of Calcium Saccharin (1 in 10) add 1 ml. of hydrochloric acid: a crystalline precipitate of saccharin is formed. Wash the precipitate well with cold water, and dry at 105° for 2 hours: it melts between 226° and 230°, page 814.

Water, page 900—Determine the water content of Calcium Saccharin by the titrimetric method: not less than 3 percent and not more than 15 percent is found.

Benzoate and salicylate—To 10 ml. of a solution of Calcium Saccharin (1 in 20), previously acidified with 5 drops of acetic acid, add 3 drops of ferric chloride T.S.: no precipitate or violet color appears.

Arsenic—A *Test Preparation* prepared with 3.33 g. of Calcium Saccharin, as directed for organic compounds, meets the requirements of the *Arsenic Test,* page 777 (3 parts per million As).

Selenium—A *Test Preparation* prepared with 200 mg. of Calcium Saccharin meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Heavy metals, page 806—Dissolve 2 g. of Calcium Saccharin in 48 ml. of water, add 2 ml. of 1 *N* hydrochloric acid, mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, then filter through a dry filter, rejecting the first 10 ml. of filtrate: the heavy metals limit for Calcium Saccharin, determined in 25 ml. of the subsequent filtrate, is 10 parts per million.

Readily carbonizable substances—Dissolve 200 mg. of Calcium Saccharin in 5 ml. of sulfuric acid T.S., and keep at a temperature of 48° to 50° for 10 minutes: the solution has no more color than Matching Fluid A (see page 856).

Assay—Weigh accurately about 500 mg. of Calcium Saccharin, and transfer completely to a separator with the aid of 10 ml. of water. Add 2 ml. of diluted hydrochloric acid, and extract the precipitated saccharin first with 30 ml., then with four 20-ml. portions, of a solvent composed of 9 volumes of chloroform and 1 volume of alcohol, filtering each extract through a small filter paper moistened with the solvent. Evaporate the combined filtrates on a steam bath, with the aid of a current of air, to dryness, then dissolve the residue in 75 ml. of hot water, cool, add 3 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 20.22 mg. of $C_{14}H_8CaN_2O_6S_2$.

Packaging and storage—Preserve Calcium Saccharin in well-closed containers.

CATEGORY—Non-nutritive sweetener.

Calcium Stearate

Calcium Stearate is a compound of calcium with a mixture of solid organic acids obtained from fats, and consists chiefly of variable proportions of calcium stearate and calcium palmitate. It contains the equivalent of not less than 9.0 percent and not more than 10.5 percent of CaO (calcium oxide).

Description—Calcium Stearate occurs as a fine, white to yellowish white, bulky powder having a slight, characteristic odor. It is unctuous and is free from grittiness.

Solubility—Calcium Stearate is insoluble in water, in alcohol, and in ether.

Identification—

A: Heat 1 g. of Calcium Stearate with a mixture of 25 ml. of water and 5 ml. of hydrochloric acid. Fatty acids are liberated and appear as an oily layer floating on the surface of the liquid. The water layer responds to the tests for *Calcium*, page 808.

B: Mix 25 g. of Calcium Stearate with 200 ml. of hot water, then add 60 ml. of diluted sulfuric acid, and heat the mixture, with frequent stirring, until the separated fatty acid layer is clear. Wash the fatty acids with boiling water until free from sulfate, collect them in a small beaker, and warm on a steam bath until the water has separated and the fatty acids are clear. Allow the acids to cool, pour off the water layer, then melt the acids, filter into a dry beaker, and dry at 105° for 20 minutes: the fatty acids so obtained congeal at a temperature not below 54° (page 814).

Loss on drying, page 814—Dry Calcium Stearate to constant weight at 105°, using 2-hour increments of heating: it loses not more than 4 percent of its weight.

Arsenic—Mix 3.3 g. of Calcium Stearate with 25 ml. of hydrochloric acid and 1 ml. of bromine T.S., and heat on a steam bath until the separated fatty acid layer is clear. Add 50 ml. of water, evaporate to about 25 ml., and filter while hot. Cool, neutralize with a solution of sodium hydroxide (1 in 2), and dilute to 35 ml. with water: this solution meets the requirements of the *Arsenic Test*, page 777 (3 parts per million As).

Heavy metals, page 806—Place 2.5 g. of Calcium Stearate in a porcelain dish, place a 500-mg. portion in a second dish for the control, and to each add 5 ml. of a solution of magnesium nitrate (1 in 4) in alcohol. Cover the dishes with 7.5 cm. short-stem funnels so that the stems are straight up. Heat for 30 minutes on a hot plate at low heat, then heat for 30 minutes at medium heat, and cool. Remove the funnels, add 20 mcg. of lead ion (Pb) to the control, and heat each dish over a suitable burner until most of the carbon is burned off. Cool, add 10 ml. of nitric acid, and transfer the solutions into 250-ml. beakers. Add 5 ml. of 70 percent perchloric acid, cautiously evaporate to dryness, then add 2 ml. of hydrochloric acid to the residues, and wash down the inside of the beakers with water. Evaporate carefully to dryness again, swirling near the dry point to avoid spattering. Repeat the hydrochloric acid treatment, then cool, and dissolve the residues in about 10 ml. of water. To each solution add 1 drop of phenolphthalein T.S. and sufficient sodium hydroxide T.S. until the solutions just turn pink, and then add diluted hydrochloric acid until the solutions become colorless. Add 1 ml. of diluted acetic acid and a small amount of charcoal to each solution, and filter through Whatman No. 2 or equivalent filter paper into 50-ml. color-comparison tubes. Wash with water, dilute to 40 ml. with water, and add 10 ml. of hydrogen sulfide T.S. to each tube: the color in the solution of the sample does not exceed that produced in the control (10 parts per million).

Assay—Boil about 1.2 g. of Calcium Stearate, accurately weighed, with 50 ml. of 0.1 *N* hydrochloric acid for 10 minutes, or until the separated fatty acid layer is clear, adding water if necessary to maintain the original volume. Cool, filter, and wash the filter and flask thoroughly with water until the last washing is not acid to litmus. Neutralize the filtrate to litmus paper with sodium hydroxide T.S. While stirring, preferably with a magnetic stirrer, titrate with 0.05 *M* disodium ethylenediaminetetraacetate as follows: add about 30 ml. from a 50-ml. buret, then add 15 ml. of sodium hydroxide T.S. and 300 mg. of hydroxy naphthol blue, and continue the titration to a blue end-point. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 2.804 mg. of CaO.

Packaging and storage—Preserve Calcium Stearate in well-closed containers.

CATEGORY—Tablet lubricant.

Calcium Sulfate

$CaSO_4$ Mol. wt. 136.14

Calcium Sulfate is anhydrous or contains two molecules of water of hydration. When dried at 250° to constant weight, it contains not less than 99.0 percent and not more than 101.0 percent of $CaSO_4$.

Description—Calcium Sulfate occurs as a fine, white to slightly yellow-white, odorless powder.

Solubility—Calcium Sulfate dissolves in diluted hydrochloric acid. It is slightly soluble in water.

Identification—Dissolve about 200 mg. of Calcium Sulfate by warming in a mixture of 4 ml. of diluted hydrochloric acid and 16 ml. of water. This solution responds to the tests for *Calcium*, page 808, and for *Sulfate*, page 810.

Loss on drying, page 814—Dry Calcium Sulfate at 250° to constant weight: the anhydrous form loses not more than 1.5 percent of its weight; the dihydrate loses not less than 17 percent and not more than 21 percent of its weight.

Carbonate—Mix 1 g. of Calcium Sulfate with 5 ml. of water, and add a few drops of diluted hydrochloric acid: no effervescence occurs when the acid is added.

Iron—Dissolve 200 mg. of Calcium Sulfate and about 50 mg. of ammonium persulfate in 10 ml. of diluted hydrochloric acid, dilute to 50 ml. with water, and mix. To this solution add 3 ml. of ammonium thiocyanate T.S., and mix thoroughly: the color obtained is no darker than that produced in 50 ml. of a solution containing 140 mcg. of ferrous ammonium sulfate (equivalent to 20 mcg. of Fe) when treated in the same manner (100 parts per million of Fe).

Heavy metals, page 806—Mix 2 g. of Calcium Sulfate with 20 ml. of water, add 25 ml. of diluted hydrochloric acid, and heat to boiling to dissolve the sample. Cool, and add stronger ammonia water to a pH of 7. Filter, evaporate to a volume of about 25 ml., and refilter if necessary to obtain a clear solution: the heavy metals limit for Calcium Sulfate is 10 parts per million.

Assay—Dissolve about 300 mg. of Calcium Sulfate, previously dried at 250° to constant weight and accurately weighed, in 100 ml. of water and 4 ml. of diluted hydrochloric acid. While stirring, preferably with a magnetic stirrer, titrate as follows: add about 30 ml. of 0.05 *M* disodium ethylenediaminetetraacetate from a 50-ml. buret, then add 15 ml. of sodium hydroxide T.S. and 300 mg. of hydroxy naphthol blue, and continue the titration to a blue endpoint. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 6.807 mg. of $CaSO_4$.

Packaging and storage—Preserve Calcium Sulfate in well-closed containers.

Labeling—The label should indicate whether the Calcium Sulfate is anhydrous or the dihydrate.

CATEGORY—Tablet diluent.

Camphor Spirit

Camphor Spirit is an alcohol solution containing, in each 100 ml., not less than 9.0 g. and not more than 11.0 g. of $C_{10}H_{16}O$.

Camphor	**100 g.**
Alcohol, a sufficient quantity,	
To make	**1000 ml.**

Dissolve the camphor in about 800 ml. of alcohol, then add alcohol to make the product measure 1000 ml. Filter if necessary.

Assay—Pipet 2.0 ml. of Camphor Spirit into a suitable pressure bottle containing 50 ml. of freshly prepared dinitrophenylhydrazine T.S. Close the pressure bottle, immerse it in a water bath, and maintain at about 75° for 4 hours. Cool to room temperature, and transfer the contents to a beaker with the aid of 100 ml. of dilute sulfuric acid (1 in 12). Allow to stand not less than 12 hours at room temperature, transfer the precipitate to a tared filter crucible, and wash with 100 ml. of dilute sulfuric acid (1 in 12) followed by 75 ml. of cold water in divided portions. Continue the suction until the excess water is removed, dry the crucible and precipitate at 80° for 2 hours, cool, and weigh. The weight of the precipitate so obtained, multiplied by 0.4581, represents the weight of $C_{10}H_{16}O$ in the sample taken.

Alcohol content, page 772—Camphor Spirit contains from 80 to 87 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Camphor Spirit in tight containers.

CATEGORY—Local irritant.

Camphorated Parachlorophenol

Camphorated Parachlorophenol contains not less than 33.0 percent and not more than 37.0 percent of C_6H_5ClO (parachlorophenol) and not less than 63.0 percent and not more than 67.0 percent of $C_{10}H_{16}O$ (camphor). The sum of the percentages of parachlorophenol and camphor is not less than 97.0 and not more than 103.0.

Parachlorophenol	**350 g.**
Camphor	**650 g.**
To make	**1000 g.**

Triturate the parachlorophenol and the camphor together until they liquefy and are thoroughly mixed.

Assay for parachlorophenol—Transfer about 1 g. of Camphorated Parachlorophenol, accurately weighed, to a wide-mouth conical flask, add a few glass beads, 6 ml. of sodium hydroxide solution (1 in 2), and 130 ml. of water. Heat the solution to boiling, add 70 ml. of potassium permanganate solution (6 in 100), and continue to boil for 20 minutes. To the hot solution, add 40 ml. of approximately 0.1 *N* silver nitrate. Add 50 ml. of 50 percent sulfuric acid, and sodium sulfite crystals, in divided portions and with swirling until the permanganate color is discharged and no manganese dioxide remains. Boil until the vapors are no longer acid to litmus, keeping the volume nearly constant by the addition of water. Add 5 ml. of nitric acid and continue to boil for 5 minutes. Cool and collect the precipitate on a tared filter crucible, wash well with water followed by 10 ml. of alcohol, dry at 105° for 1 hour, cool, and weigh. Each g. of silver chloride is equivalent to 897.0 mg. of C_6H_5ClO.

Assay for camphor—Transfer about 300 mg. of Camphorated Parachlorophenol, accurately weighed, into a 200-ml. pressure bottle containing 50 ml. of freshly prepared dinitrophenylhydrazine T.S. Close the pressure bottle, immerse it in a water bath, and maintain at about 75° for 4 hours. Cool to room temperature, then transfer the contents to a beaker with the aid of 100 ml. of dilute sulfuric acid (1 in 12), and allow it to stand overnight. Collect the precipitate on a tared filter crucible, wash with 100 ml. of dilute sulfuric acid (1 in 12) and then with 75 ml. of cold water, in divided portions, to remove the acid. Dry for 2 hours at 80°, cool, and weigh. The weight of the precipitate so obtained, multiplied by 0.4581, represents the weight of $C_{10}H_{16}O$ in the sample taken.

Packaging and storage—Preserve Camphorated Parachlorophenol in tight, light-resistant containers.

Category—Local anti-infective (dental).

Candicidin

Candicidin is a substance produced by the growth of *Streptomyces griseus* Waksman and Henrici (Fam. *Streptomycetaceæ*). Candicidin, dried at 40° for 3 hours at a pressure of 5 mm. or less of mercury, has a potency of not less than 1000 mcg. per mg. Candicidin conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Candicidin occurs as a yellow to brown powder.

Solubility—Candicidin is sparingly soluble in water, and is very slightly soluble in alcohol, in acetone, and in *n*-butanol.

Packaging and storage—Preserve Candicidin in tight containers, in a refrigerator.

Category—Local antifungal.

Application—Vaginal, **3 mg.** inserted twice daily for 14 days.

Candicidin Ointment

Candicidin Ointment is candicidin dispersed in a suitable ointment base. It contains not less than 90.0 percent and not more than 140.0 percent of the labeled amount of candicidin. Candicidin Ointment conforms to the regulations of the federal

Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Candicidin Ointment in well-closed containers, in a refrigerator.

Ointment available—Candicidin Ointment usually available contains 0.06 percent of candicidin.

Category and Application—See Candicidin.

Candicidin Suppositories

Candicidin Suppositories contain not less than 90.0 percent and not more than 140.0 percent of the labeled amount of candicidin. Candicidin Suppositories conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Candicidin Suppositories in tight containers, in a refrigerator.

Suppositories available—Candicidin Suppositories usually available contain the following amount of candicidin: 3 mg.

Category and Application—See Candicidin.

Caramel

Caramel is a concentrated solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark brown mass results, a small amount of alkali, alkaline carbonate, or a trace of mineral acid being added while heating.

Description—Caramel is a thick, dark brown liquid with the characteristic odor of burnt sugar, and a pleasant, bitter taste. One part of Caramel dissolved in 1000 parts of water yields a clear solution having a distinct yellowish orange color. The color of this solution is not changed and no precipitate is formed after exposure to sunlight for 6 hours. Caramel spread in a thin layer on a glass plate appears homogeneous, reddish brown, and transparent.

Solubility—Caramel is miscible with water and is soluble in dilute alcohol up to 55 percent (v/v). It is immiscible with ether, chloroform, acetone, benzene, and solvent hexane.

Specific gravity, page 866—The specific gravity of Caramel is not less than 1.30.

Purity—The addition of 0.5 ml. of phosphoric acid to 20 ml. of a solution of Caramel (1 in 20) produces no precipitate.

Ash—Caramel swells when incinerated, and forms a coke-like charcoal which burns off only after prolonged heating at a high temperature. It yields not more than 8 percent of ash.

Packaging and storage—Preserve Caramel in tight containers.

Category—Color.

Caraway

Caraway is the dried ripe fruit of *Carum carvi* Linné (Fam. *Umbelliferæ*).

Unground Caraway occurs chiefly as separated mericarps from about 4 mm. up to about 7 mm. in length and from 1 to 2 mm. in diameter. The mericarp is oblong, curved, and tapers toward base and apex to which half of the stylopodium is attached. Externally, it is dark brown to weak brown and shows 5 lighter-colored, filiform primary ribs, between each pair of which, on the dorsal surface, occurs a secondary rib. The odor and taste are characteristically aromatic.

Histology—The mericarp of Caraway is nearly equilaterally pentagonal in transverse section and shows a fibrovascular bundle in each primary rib. The epicarp consists of tabular-polygonal epidermal cells with thick outer walls possessing a striated cuticle and with occasional stomata. The mesocarp, each located between primary rib regions, is composed of collapsed, thin-walled parenchyma normally bearing 4 dorsal vittæ in the intervals and 2 commissural vittæ, sometimes one or more additional. The endocarp consists of broad, slightly undulate, inner epidermal cross cells which are coherent with the collapsed cells of the spermoderm. The endosperm consists of thick-walled reserve parenchyma containing fixed oil and aleurone grains up to 10 μ in diameter, the latter with embedded rosette aggregates of calcium oxalate up to 4 μ in diameter. An embryo is embedded in the upper end of the endosperm.

Powdered Caraway is moderate yellowish brown to light olive-brown. It shows fragments of the epicarp with striped cuticle; numerous polyhedral endosperm cells containing aleurone grains with embedded calcium oxalate rosette aggregates; few fragments of slightly lignified fibers and spiral vessels; fragments of cross cells of endocarp; orange to yellow fragments of vittæ; no reticulate parenchyma.

Acid-insoluble ash, page 886—Caraway yields not more than 1.5 percent of acid-insoluble ash.

Foreign organic matter, page 886—The amount of other fruits, seeds, or other foreign organic matter in Caraway does not exceed 3 percent.

Packaging and storage—Preserve Caraway in well-closed containers. Caraway is susceptible to attack by insects, page 14.

CATEGORY—Flavor.

Caraway Oil

Caraway Oil is a volatile oil distilled from the dried, ripe fruit of *Carum carvi* Linné (Fam. *Umbelliferæ*). Caraway Oil yields not less than 50.0 percent (v/v) of $C_{10}H_{14}O$ (carvone).

Description—Caraway Oil is a colorless to pale yellow liquid, with the characteristic odor and taste of caraway.

Solubility test—One volume of Caraway Oil is soluble in 8 volumes of 80 percent alcohol.

Specific gravity, page 866—The specific gravity of Caraway Oil is not less than 0.900 and not more than 0.910.

Angular rotation, page 822—The angular rotation of Caraway Oil is not less than +70° and not more than +80° when determined in a 100-mm. tube.

Refractive index, page 858—The refractive index of Caraway Oil at 20° is not less than 1.484 and not more than 1.488.

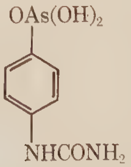
Heavy metals, page 806—Caraway Oil meets the requirements of the test for heavy metals in volatile oils.

Assay—Introduce 10 ml. of Caraway Oil, accurately measured, into a cassia flask, and add 50 ml. of a saturated solution of sodium sulfite which has been rendered neutral to 2 drops of phenolphthalein T.S. by means of a saturated sodium bisulfite solution. Heat the flask in boiling water, and shake it repeatedly, neutralizing the mixture from time to time by the addition of a few drops of the saturated sodium bisulfite solution. When no coloration appears upon adding a few more drops of phenolphthalein T.S. and heating for 15 minutes, cool the mixture to room temperature, and when the liquids have separated completely, add sufficient sodium sulfite solution to raise the lower level of the oily layer within the graduated portion of the neck of the flask. Note the volume of the residual oily liquid. This volume does not exceed 5 ml., indicating the presence in Caraway Oil of not less than 50.0 percent (v/v) of $C_{10}H_{14}O$ (carvone).

Packaging and storage—Preserve Caraway Oil in tight, light-resistant containers.

CATEGORY—Flavor.

Carbarsone



N-Carbamoylarsanilic Acid

$C_7H_9AsN_2O_4$ Mol. wt. 260.08

Carbarsone contains not less than 97.5 percent and not more than 101.0 percent of $C_7H_9AsN_2O_4$, calculated on the dried basis.

Description—Carbarsone occurs as a white, almost odorless powder, having a slightly acid taste. Its saturated solution is acid to litmus.

Solubility—Carbarsone is slightly soluble in water and in alcohol and is very slightly soluble in chloroform and in ether. It is soluble in solutions of alkali hydroxides and carbonates.

Identification—

A: Warm about 500 mg. of Carbarsone in a test tube with 5 ml. of sodium hydroxide solution (1 in 5): a piece of moistened red litmus paper held over the mouth of the tube turns blue.

B: Dissolve about 1 g. of Carbarsone in a mixture of 10 ml. of sodium hydroxide T.S. and 10 ml. of water, add 2 g. of sodium hydrosulfite, and warm the mixture to 50°: a light yellow precipitate is formed, which is insoluble in an excess of sodium hydroxide T.S.

C: Acidify a portion of the solution obtained in the *Assay* with hydrochloric acid, and add hydrogen sulfide T.S.: a yellow precipitate of arsenic sulfide is formed, which is soluble in ammonium carbonate T.S.

Loss on drying, page 814—Dry Carbarsone at 80° for 6 hours: it loses not more than 1.5 percent of its weight.

Free arsanilic acid—Transfer 125 mg. of Carbarsone, accurately weighed, to a 250-ml. volumetric flask, dissolve in a minimum volume of sodium hydroxide solution (1 in 1000), dilute to volume with water, and mix. Pipet 5.0 ml. of this solution into a 25-ml. volumetric flask, add 0.5 ml. of diluted hydrochloric acid, chill in an ice bath, add 2 ml. of sodium nitrite solution (1 in 1000), and cool for 3 minutes. Add 2 ml. of ammonium sulfamate solution (1 in 100), mix, and return to the ice bath for 1 minute. Add 1 ml. of *N*-1-naphthyl ethylenediamine dihydrochloride solution (prepared by dissolving 50 mg. of the reagent in 15 ml. of water, adding 35 ml. of propylene glycol, and mixing), mix, and dilute to volume with water. Determine the absorbance of the solution, with a suitable spectrophotometer, at the maximum at about 538 mμ: the absorbance does not exceed that of 5 ml. of a solution of arsanilic acid prepared with the aid of sodium hydroxide solution (1 in 1000) to contain 5 mcg. in each ml. and treated as directed above, beginning with "Pipet 5.0 ml. of the solution . . . ." (1.0 percent).

Arsenate—Dissolve 500 mg. of Carbarsone in 2 ml. of ammonia T.S., dilute to 5 ml., add 3 ml. of magnesia mixture T.S., and shake vigorously: no precipitate forms within 30 minutes.

Assay—Transfer about 250 mg. of Carbarsone accurately weighed, to a small Kjeldahl flask. Add 10 g. of potassium sulfate and 20 ml. of sulfuric acid, and swirl the acid so that the Carbarsone is thoroughly wetted. Slowly digest the mixture over a low flame, keeping the temperature below the boiling point, until the solution becomes colorless. Cool, cautiously add 150 ml. of water, then add a saturated solution of sodium hydroxide until the solution is slightly alkaline to litmus, keeping the flask under cool water. Cautiously render the solution slightly acid with diluted sulfuric acid, and allow to cool. Add to the solution a small excess (1.5 g.) of sodium bicarbonate, swirl to dissolve, and titrate with 0.1 *N* iodine, adding starch T.S. as the end-point is neared. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* iodine is equivalent to 13.00 mg. of $C_7H_9AsN_2O_4$.

Packaging and storage—Preserve Carbarsone in well-closed containers.

Category—Antiamebic.

Usual dose—**250 mg.** two or three times a day for 10 days.

Usual dose range—**100 to 250 mg.**

Carbarsone Capsules

Carbarsone Capsules contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_7H_9AsN_2O_4$.

Identification—Add 10 ml. of sodium hydroxide T.S., and 10 ml. of water to about 1 g. of the contents of Carbarsone Capsules, shake well for a few minutes, and filter. To the clear filtrate add 2 g. of sodium hydrosulfite, and warm to 50°: a light yellow precipitate, which is insoluble in an excess of sodium hydroxide T.S., is formed.

Weight variation, page 901—Carbarsone Capsules meet the requirements of the weight variation test for capsules.

Assay—Transfer, as completely as possible, the contents of not less than 20 Carbarsone Capsules to a small tared dish, and weigh. Mix well with a glass rod or spatula, then transfer an accurately weighed portion of the powder, equivalent to about 250 mg. of carbarsone, to a small Kjeldahl flask. Add 10 g. of potassium sulfate and 20 ml. of sulfuric acid and swirl the acid so that the carbarsone is thoroughly wetted. Slowly digest the mixture over a low flame, keeping the temperature below the boiling point, until the solution becomes colorless. Cool, cautiously add 150 ml. of water, then add a saturated solution of sodium hydroxide until the solution is slightly alkaline to litmus paper, keeping the flask under cool water. Cautiously render the solution slightly acid with diluted sulfuric acid, and allow to cool. Dissolve in the solution a small excess (1.5 g.) of sodium bicarbonate, and titrate with 0.1 *N* iodine, using starch T.S. if desired. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* iodine is equivalent to 13.00 mg. of $C_7H_9AsN_2O_4$.

Packaging and storage—Preserve Carbarsone Capsules in well-closed containers.

Capsules available—Carbarsone Capsules usually available contain the following amount of carbarsone: 250 mg.

CATEGORY and DOSE—See Carbarsone.

Carbarsone Tablets

Carbarsone Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_7H_9AsN_2O_4$.

Identification—Add 10 ml. of sodium hydroxide T.S. and 10 ml. of water to about 1 g. of powdered Carbarsone Tablets, shake well for a few minutes, and filter. To the clear filtrate add 2 g. of sodium hydrosulfite, and warm to 50°: a light yellow precipitate is formed, which is insoluble in an excess of sodium hydroxide T.S.

Disintegration, page 878—The disintegration time limit for Carbarsone Tablets is 30 minutes.

Weight variation, page 901—Carbarsone Tablets meet the requirements of the weight variation test for tablets.

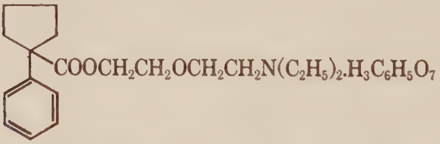
Assay—Weigh and finely powder not less than 20 Carbarsone Tablets. Weigh accurately a portion of the powder, equivalent to about 250 mg. of carbarsone, transfer to a small Kjeldahl flask, and proceed as directed in the *Assay* under *Carbarsone,* page 134, beginning with "Add 10 g. of potassium sulfate . . . ."

Packaging and storage—Preserve Carbarsone Tablets in well-closed containers.

Tablets available—Carbarsone Tablets usually available contain the following amount of carbarsone: 250 mg.

CATEGORY and DOSE—See Carbarsone.

Carbetapentane Citrate



2-[2-(Diethylamino)ethoxy]ethyl 1-Phenylcyclopentanecarboxylate Citrate (1:1)

$C_{20}H_{31}NO_3 . C_6H_8O_7$ Mol. wt. 525.60

Carbetapentane Citrate contains not less than 98.0 percent and not more than 100.5 percent of $C_{20}H_{31}NO_3 . C_6H_8O_7$, calculated on the anhydrous basis.

Description—Carbetapentane Citrate occurs as a white, or practically white, odorless, crystalline powder.

Solubility—Carbetapentane Citrate is freely soluble in water and in chloroform, slightly soluble in alcohol, and practically insoluble in ether.

Melting range, *Class Ia,* page 815—Carbetapentane Citrate melts between 90° and 95°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Carbetapentane Citrate, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Carbetapentane Citrate Reference Standard, similarly measured.

Water, page 900—Determine the water content of Carbetapentane Citrate by the titrimetric method: not more than 1 percent of water is found.

Residue on ignition, page 858—Carbetapentane Citrate yields not more than 0.5 percent of residue on ignition. Retain the residue from a 1-g. sample for the *Heavy metals test.*

Heavy metals, page 806—Dissolve the residue from *Residue on ignition* in nitric acid and evaporate to dryness. Add 10 ml. of ammonium acetate T.S., and digest in a covered crucible on a steam bath for

30 minutes. Filter, and wash the residue with sufficient water to make 25 ml.: the heavy metals limit for Carbetapentane Citrate is 25 parts per million.

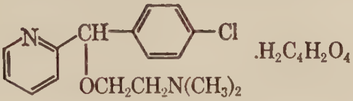
Assay—Dissolve about 250 mg. of Carbetapentane Citrate, accurately weighed, in 10 ml. of chloroform. Add 50 ml. of glacial acetic acid, 5 ml. of acetic anhydride, and 5 drops of a solution of quinaldine red in glacial acetic acid (1 in 1000), and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 52.56 mg. of $C_{20}H_{31}NO_3 . C_6H_8O_7$.

Packaging and storage—Preserve Carbetapentane Citrate in tight containers.

CATEGORY—Antitussive.

USUAL DOSE—**15** to **30 mg.** three to four times a day.

Carbinoxamine Maleate*



2-[*p*-Chloro-α-[2-(dimethylamino)ethoxy]benzyl]pyridine Maleate (1:1)

$C_{16}H_{19}ClN_2O . C_4H_4O_4$ Mol. wt. 406.87

Carbinoxamine Maleate, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{16}H_{19}ClN_2O . C_4H_4O_4$.

Description—Carbinoxamine Maleate occurs as a white, odorless, crystalline powder.

Solubility—Carbinoxamine Maleate is very soluble in water, freely soluble in alcohol and in chloroform, and very slightly soluble in ether.

Melting range, *Class Ia,* page 815—Carbinoxamine Maleate, previously dried at 105° for 2 hours, melts between 116° and 121°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Carbinoxamine Maleate, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Carbinoxamine Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Carbinoxamine Maleate in methanol exhibits maxima and minima at the same wavelengths as that of NF Carbinoxamine Maleate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 260 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Carbinoxamine Maleate (1 in 100) is between 4.6 and 5.1.

Loss on drying, page 814—Dry Carbinoxamine Maleate at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Carbinoxamine Maleate yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 400 mg. of Carbinoxamine Maleate, previously dried at 105° for 2 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 20.34 mg. of $C_{16}H_{19}ClN_2O . C_4H_4O_4$.

Packaging and storage—Preserve Carbinoxamine Maleate in tight, light-resistant containers.

CATEGORY—Antihistaminic.

USUAL DOSE—**4 mg.** three or four times a day.

USUAL DOSE RANGE—**4** to **8 mg.**

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* Patented. See notice, page ii.

Carbinoxamine Maleate Elixir

Carbinoxamine Maleate Elixir contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{16}H_{19}ClN_2O . C_4H_4O_4$.

Identification—A 1 in 50,000 solution of carbinoxamine maleate in 0.5 *N* sulfuric acid prepared from Carbinoxamine Maleate Elixir as directed under *Salts of Organic Nitrogenous Bases*, page 865, exhibits an absorbance maximum at 263 ± 2 mμ. The absorptivity at 263 mμ is within 7 percent of that of a 1 in 50,000 solution of NF Carbinoxamine Maleate Reference Standard in 0.5 *N* sulfuric acid, similarly measured.

pH, page 824—The pH of Carbinoxamine Maleate Elixir is between 5.0 and 6.7.

Assay—Transfer an accurately measured volume of Carbinoxamine Maleate Elixir, equivalent to about 80 mg. of carbinoxamine maleate, to a 250-ml. separator, add 4 g. of sodium bicarbonate, and mix. Extract with five 20-ml. portions of chloroform, and filter the extracts into a beaker through a small pledget of cotton. Evaporate the combined chloroform extracts to about 50 ml. on a steam bath, and add 50 ml. of glacial acetic acid. Add 1 drop of crystal violet T.S., and titrate with 0.05 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Each ml. of 0.05 *N* perchloric acid is equivalent to 10.17 mg. of $C_{16}H_{19}ClN_2O . C_4H_4O_4$.

Alcohol content, page 772—Carbinoxamine Maleate Elixir contains from 6.5 to 8 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Carbinoxamine Maleate in tight, light-resistant containers.

Elixir available—Carbinoxamine Maleate Elixir usually available contains the following amount of carbinoxamine maleate: 4 mg. in 5 ml.

CATEGORY and DOSE—See Carbinoxamine Maleate.

Carbinoxamine Maleate Tablets

Carbinoxamine Maleate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{16}H_{19}ClN_2O . C_4H_4O_4$.

Identification—A 1 in 50,000 solution of carbinoxamine maleate in 0.5 *N* sulfuric acid prepared from Carbinoxamine Maleate Tablets as directed under *Salts of Organic Nitrogenous Bases*, page 865, exhibits an absorbance maximum at 263 ± 2 mμ. The absorptivity of the solution at 263 mμ is within 7 percent of that of a 1 in 50,000 solution of NF Carbinoxamine Maleate Reference Standard in 0.5 *N* sulfuric acid, similarly measured.

Disintegration, page 878—The disintegration time limit for Carbinoxamine Maleate Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Carbinoxamine Maleate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Place one tablet in a 100-ml. volumetric flask, add 10 ml. of water, and shake mechanically for 15 minutes. Dilute to volume with methanol, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol-water mixture (9:1) to provide a solution containing approximately 40 mcg. of carbinoxamine maleate per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Carbinoxamine Maleate Reference Standard, in the same medium, at a concentration of about 40 mcg. per ml., in 1-cm. cells, at the maximum at about 260 mμ, with a suitable spectrophotometer, using methanol-water mixture (9:1) as the blank. Calculate the quantity, in mg., of $C_{16}H_{19}ClN_2O.C_4H_4O_4$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of carbinoxamine maleate, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of carbinoxamine maleate in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Carbinoxamine Maleate Tablets. Transfer to a separator an accurately weighed portion of the powder, equivalent to about 100 mg. of carbinoxamine maleate, add 35 ml. of water and 3 g. of sodium bicarbonate, and mix. Extract with one 30-ml. portion, two 20-ml. portions, and two 15-ml. portions of chloroform, filtering the extracts through a pledget of cotton. Evaporate the combined chloroform extracts just to dryness on a steam bath, dissolve the residue in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.05 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.05 *N* perchloric acid is equivalent to 10.17 mg. of $C_{16}H_{19}ClN_2O . C_4H_4O_4$.

Packaging and storage—Preserve Carbinoxamine Maleate Tablets in tight, light-resistant containers.

Tablets available—Carbinoxamine Maleate Tablets usually available contain the following amount of carbinoxamine maleate: 4 mg.

CATEGORY and DOSE—See Carbinoxamine Maleate.

Carbol-Fuchsin Solution

Basic Fuchsin	**3 g.**
Phenol	**45 g.**
Resorcinol	**100 g.**
Acetone	**50 ml.**
Alcohol	**100 ml.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Dissolve the basic fuchsin in a mixture of the acetone and alcohol, and add to this solution the phenol and resorcinol previously dissolved in 725 ml. of purified water. Then, add sufficient purified water to make the product measure 1000 ml. Mix thoroughly.

Description—Carbol-Fuchsin Solution is a dark purple liquid which appears purplish red when spread in a thin film.

Specific gravity, page 866—The specific gravity of Carbol-Fuchsin Solution is not less than 0.990 and not more than 1.050.

Alcohol content, page 772—Carbol-Fuchsin Solution contains from 7 to 10 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Carbol-Fuchsin Solution in tight, light-resistant containers.

CATEGORY—Local antifungal.

FOR EXTERNAL USE—Topically, apply undiluted once or twice daily.

Carboxymethylcellulose, Sodium, Tablets, page 640

Cardamom Seed

Cardamom Seed is the dried ripe seed of *Elettaria cardamomum* (Linné) Maton (Fam. *Zingiberaceæ*).

Cardamom Seed should be recently removed from the capsule.

Unground Cardamom Seed occurs usually in agglutinated groups of 2 to 7 seeds and as separate seeds surrounded by an adhering membranous aril. The individual seeds are oblong-ovoid or irregularly 3- to 4-sided, from 3 to 4 mm. in length; convex on the dorsal side, strongly longitudinally grooved on the ventral side and coarsely tuberculated; externally pale orange to dark brown. The odor is aromatic. The taste is aromatic, pungent, and slightly bitter.

Histology—Sections of Cardamom Seed show a loosely attached membranous aril; a brownish seed-coat consisting of an epidermal layer of thick-walled cells, a pigment layer of small cells with red to orange contents, a layer of volatile oil cells with suberized walls and a single layer of radially elongated, strongly lignified stone cells with inner walls heavily thickened, and a minute lumen containing silica; a large, colorless perisperm surrounding a central, orange to yellow endosperm in which a small straight embryo is embedded.

Powdered Cardamom Seed is brown to weak yellow to light olive-green. It consists chiefly of fragments of perisperm, endosperm, embryo, and seed-coat. The endosperm and perisperm cells are filled with starch grains from 1 to 4 μ in diameter or may contain one or more prisms of calcium oxalate from 10 to 25 μ in diameter. The seed-coat is characterized by its red to orange colored cells, polygonal in surface view and about 20 μ in diameter. Fragments of pericarp tissue with spiral vessels and with accompanying slightly lignified fibers are relatively few.

Acid-insoluble ash, page 886—Cardamom Seed yields not more than 4 percent of acid-insoluble ash.

Packaging and storage—Preserve Cardamom Seed against attack by insects, page 14.

CATEGORY—Flavor.

Compound Cardamom Tincture

Cardamom Seed, in moderately coarse powder	20 g.
Cinnamon, in fine powder	25 g.
Caraway, in moderately coarse powder	12 g.
To make	1000 ml.

Prepare a tincture by Process M, page 838, macerating the mixed powders in 750 ml. of a mixture of 50 ml. of glycerin and 950 ml. of diluted alcohol, and completing the preparation by using first the remainder of the mixture of alcohol and glycerin prepared as directed above, and then diluted alcohol.

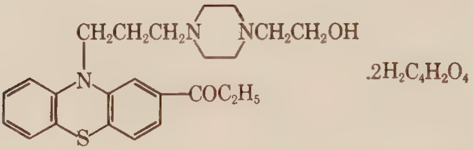
NOTE: Compound Cardamom Tincture may be colored with one or more colors (see page 8).

Alcohol content, page 772—Compound Cardamom Tincture contains from 43 to 47 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Compound Cardamom Tincture in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat.

CATEGORY—Flavor.

Carphenazine Maleate*



1-[10-[3-[4-(2-Hydroxyethyl)-1-piperazinyl]-propyl]phenothiazin-2-yl]-1-propanone Maleate (1:2)

$C_{24}H_{31}N_3O_2S.2C_4H_4O_4$ Mol. wt. 657.75

Carphenazine Maleate contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{31}N_3O_2S.2C_4H_4O_4$, calculated on the anhydrous basis.

Description—Carphenazine Maleate occurs as a yellow, finely divided, odorless powder.

Solubility—Carphenazine Maleate is slightly soluble in alcohol and in water. It is practically insoluble in ether.

Identification—

A: Dissolve about 15 mg. of Carphenazine Maleate in 10 ml. of water, place 5 drops of the solution on a spot plate, and add 1 drop of a solution of chloramine T (1 in 10): a violet precipitate forms, slowly changing to gray. To another 5 drops of the solution add 1 drop of *Buffered palladous chloride solution,* prepared as directed in the *Assay:* a red color develops.

B: Dissolve about 15 mg. of Carphenazine Maleate in 10 ml. of alcohol, and place 1 drop of the solution on a piece of filter paper. Allow the solvent to evaporate, and examine the residue under a shortwave ultraviolet lamp: a yellow fluorescence is observed.

Melting range, *Class Ia,* page 815—Carphenazine Maleate melts between 162° and 167°, with decomposition.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Carphenazine Maleate, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Carphenazine Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Carphenazine Maleate in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Carphenazine Maleate Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance occurring at about 243 $m\mu$, do not differ by more than 3 percent.

pH, page 824—The pH of a 1 in 100 suspension in water of Carphenazine Maleate is between 2.5 and 3.5.

Water, page 900—Determine the water content of Carphenazine Maleate by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Carphenazine Maleate yields not more than 0.2 percent of residue on ignition.

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* Patented. See notice, page ii.

Assay—

Buffered palladous chloride solution—Transfer 500 mg. of palladous chloride to a 250-ml. beaker, add 5 ml. of hydrochloric acid, and warm on a steam bath. Add 200 ml. of hot water in small portions, and continue heating until solution is complete. Cool, dilute to 500.0 ml. with water, and mix. Transfer 75.0 ml. of this solution to a 500-ml. volumetric flask, add 50 ml. of 1 *N* sodium acetate and 44 ml. of 1 *N* hydrochloric acid, dilute to volume with water, and mix.

Standard preparation—Transfer about 50 mg. of NF Carphenazine Maleate Reference Standard, accurately weighed, to a 250-ml. volumetric flask, add diluted alcohol to volume, and mix.

Assay preparation—Transfer about 50 mg. of Carphenazine Maleate, accurately weighed, to a 250-ml. volumetric flask, add diluted alcohol to volume, and mix.

Procedure—Transfer 3.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of diluted alcohol to serve as the blank to separate glass-stoppered tubes. To each tube add 4.0 ml. of *Buffered palladous chloride solution*, and mix. Within 10 minutes, concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 490 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{24}H_{31}N_3O_2S.2C_4H_4O_4$ in the Carphenazine Maleate taken by the formula $0.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Carphenazine Maleate in tight, light-resistant containers.

CATEGORY—Tranquilizer (major).

USUAL DOSE RANGE—**12.5** to **50 mg.** three times a day; increased by **12.5** to **50 mg.** daily at intervals of from 4 days to 1 week. The maximal daily dose recommended is 400 mg.

Carphenazine Maleate Tablets

Carphenazine Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{24}H_{31}N_3O_2S . 2C_4H_4O_4$.

Identification—Transfer to a glass-stoppered flask an amount of powdered Carphenazine Maleate Tablets, equivalent to about 25 mg. of carphenazine maleate, add 100 ml. of alcohol, and shake occasionally during 15 minutes. Filter through a medium-porosity sintered-glass filter, discarding the first 20 ml. of filtrate. Evaporate 6 ml. of the subsequent filtrate to dryness on a water bath with the aid of a current of air, and dissolve the residue in 1 ml. of water: the solution responds to the *Identification tests* under *Carphenazine Maleate*, page 140.

Disintegration, page 878—The disintegration time limit for Carphenazine Maleate Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Carphenazine Maleate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Carphenazine Maleate*, page 140.

Assay preparation—Weigh and finely powder not less than 20 Carphenazine Maleate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of carphenazine maleate, to a medium-porosity sintered-glass funnel, and extract the powder with successive 5-ml. portions of alcohol, using suction and collecting the extracts in a 100-ml. volumetric flask containing 50 ml. of water. Dilute to volume with alcohol, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Carphenazine Maleate*, page 140. Calculate the quantity, in mg., of $C_{24}H_{31}N_3O_2S.2C_4H_4O_4$ in the portion of Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Carphenazine Maleate Tablets in tight, light-resistant containers.

Tablets available—Carphenazine Maleate Tablets usually available contain the following amounts of carphenazine maleate: 12.5, 25, and 50 mg.

CATEGORY and DOSE—See Carphenazine Maleate.

Cascara Tablets

Cascara Tablets are prepared from cascara sagrada extract.

Disintegration, page 878—The disintegration time limit for Cascara Tablets is 60 minutes.

Weight variation, page 901—Cascara Tablets meet the requirements of the weight variation test for tablets.

Packaging and storage—Preserve Cascara Tablets in tight containers. If the Tablets are coated, well-closed containers may be used.

Tablets available—Cascara Tablets usually available contain the following amounts of cascara sagrada extract: 120, 200, and 300 mg.

CATEGORY and DOSE—See Cascara Sagrada Extract.

Cascara Sagrada Extract

One g. of Cascara Sagrada Extract represents 3 g. of cascara sagrada.

Mix 900 g. of cascara sagrada, in coarse powder, with 4000 ml. of boiling water, and macerate the mixture during 3 hours. Then transfer it to a percolator, allow it to drain, and exhaust it by percolation, using boiling water as the menstruum, and collecting about 5000 ml. of percolate. Evaporate the percolate to dryness, reduce the extract to a fine powder, and add sufficient starch, dried at 100°, to make the product weigh 300 g. Mix the powders thoroughly, and pass the Extract through a fine sieve.

Packaging and storage—Preserve Cascara Sagrada Extract in tight, light-resistant containers, preferably at a temperature not above 30°.

CATEGORY—Cathartic.
USUAL DOSE—**300 mg.**

Cascara Sagrada Fluidextract

Cascara Sagrada, in very coarse powder	**1000 g.**

Prepare a fluidextract by Process D, page 830. Evaporate the percolate until it measures 800 ml., and when it is cold, gradually add 200 ml. of alcohol and, if necessary, sufficient water to make the product measure 1000 ml. Mix thoroughly.

Alcohol content, page 772—Cascara Sagrada Fluidextract contains from 17 to 19 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Cascara Sagrada Fluidextract in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat.

CATEGORY—Cathartic.
USUAL DOSE—**1 ml.**

Aromatic Castor Oil

Cinnamon Oil	**3 ml.**
Clove Oil	**1 ml.**
Saccharin	**500 mg.**
Vanillin	**1 g.**
Alcohol	**30 ml.**
Castor Oil, a sufficient quantity,	
To make	**1000 ml.**

Dissolve the volatile oils and the solids in the alcohol, add the castor oil, and mix thoroughly.

Alcohol content, page 772—Aromatic Castor Oil contains from 2 to 3 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Aromatic Castor Oil in tight containers.

CATEGORY—Cathartic.
USUAL DOSE—**15 ml.**

Microcrystalline Cellulose

Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Description—Microcrystalline Cellulose occurs as a fine, white, odorless, crystalline powder. It consists of free-flowing, nonfibrous particles which may be compressed into self-binding tablets which disintegrate rapidly in water.

Solubility—Microcrystalline Cellulose is insoluble in water, in dilute acids, and in most organic solvents. It is slightly soluble in sodium hydroxide solution (1 in 20).

Identification—Mix 30 g. of Microcrystalline Cellulose with 270 ml. of water in a high-speed (18,000 r.p.m.) power blender for 5 minutes. Transfer 100 ml. of the mixture to a 100-ml. graduated cylinder, and allow to stand for 3 hours: a white, opaque, bubble-free dispersion, which does not form a supernatant liquid at the surface, is obtained.

pH, page 824—Shake about 5 g. of Microcrystalline Cellulose with 40 ml. of water for 20 minutes, and centrifuge: the pH of the supernatant liquid is between 5.5 and 7.0.

Loss on drying, page 814—Dry Microcrystalline Cellulose at 105° for 3 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Microcrystalline Cellulose yields not more than 0.05 percent of residue on ignition.

Water-soluble substances—Shake 5 g. of Microcrystalline Cellulose with about 80 ml. of water for 10 minutes, filter through Whatman No. 42 or equivalent filter paper into a tared beaker, evaporate to dryness on a steam bath, and dry at 105° for 1 hour: not more than 8 mg. of residue is obtained (0.16 percent).

Heavy metals, *Method II,* page 806—The heavy metals limit for Microcrystalline Cellulose is 10 parts per million.

Starch—To 20 ml. of the dispersion of Microcrystalline Cellulose obtained in the *Identification test,* add a few drops of iodine T.S., and mix: no purplish to blue or blue color is produced.

Packaging and storage—Preserve Microcrystalline Cellulose in well-closed containers.

CATEGORY—Tablet diluent.

Cetyl Alcohol

$CH_3(CH_2)_{14}CH_2OH$

1-Hexadecanol

$C_{16}H_{34}O$ Mol. wt. 242.45

Cetyl Alcohol is a mixture of solid alcohols consisting chiefly of cetyl alcohol.

Description—Cetyl Alcohol occurs as unctuous, white flakes, granules, cubes, or castings. It has a faint characteristic odor and a bland, mild taste.

Solubility—Cetyl Alcohol dissolves in alcohol and in ether, the solubility increasing with an increase in temperature. It is insoluble in water.

Melting range, page 814—Cetyl Alcohol melts between 45° and 50°, by a *Class I* procedure, except that the sample is inserted into the bath at about room temperature.

Acid value, page 804—The acid value of Cetyl Alcohol is not more than 2.

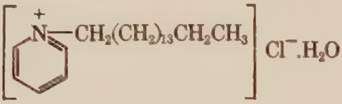
Iodine value, page 804—The iodine value of Cetyl Alcohol is not more than 5.

Hydroxyl number—Transfer into a dry 250-ml. iodine flask about 2 g. of Cetyl Alcohol, accurately weighed, and add 2.0 ml. of pyridine followed by 10 ml. of toluene, using the latter to rinse the neck of the flask. To the mixture add 10.0 ml. of approximately 1.5 *M* acetyl chloride in toluene, stopper the flask and immerse in a water bath at 60° to 65° for 20 minutes. Add 25 ml. of water, stopper the flask, shake it vigorously for 1 or 2 minutes, and allow to stand for 5 minutes to decompose the excess acetyl chloride. Add 1 ml. of phenolphthalein T.S., and titrate with 1 *N* sodium hydroxide to a permanent pink endpoint, shaking the flask vigorously toward the end of the titration to maintain the contents in an emulsified condition. Run a blank under identical conditions, using the same amounts of reagents as in the determination. Subtract the number of ml. of 1 *N* sodium hydroxide used for the sample from the number of ml. used for the blank. Multiply the difference by 56.11 and divide by the weight of sample to obtain the hydroxyl number, which is the number of mg. of potassium hydroxide equivalent to the hydroxyl content of 1 g. of the sample. The hydroxyl number of Cetyl Alcohol is not less than 218 and not more than 238.

Packaging and storage—Preserve Cetyl Alcohol in well-closed containers.

CATEGORY—Emulsifying and stiffening agent.

Cetylpyridinium Chloride



1-Hexadecylpyridinium Chloride

$C_{21}H_{38}ClN \, . \, H_2O$ Mol. wt. 358.01

Cetylpyridinium Chloride contains not less than 99.0 percent and not more than 102.0 percent of $C_{21}H_{38}ClN$, calculated on the anhydrous basis.

Description—Cetylpyridinium Chloride occurs as a white powder having a slight, characteristic odor.

Solubility—Cetylpyridinium Chloride is very soluble in water, in alcohol, and in chloroform. It is slightly soluble in benzene and in ether.

Identification—

A: Heat about 250 mg. of Cetylpyridinium Chloride in a test tube until it melts and a brown color develops: the odor of pyridine becomes perceptible.

B: Dissolve 100 mg. of Cetylpyridinium Chloride in 50 ml. of water: a 10-ml. portion of the solution responds to the tests for *Chloride*, page 808, except a turbidity is produced, rather than a curdy white precipitate, when the silver nitrate T.S. is added.

C: To 10 ml. of the solution prepared in *Identification test B* add 10 ml. of 0.01 *M* potassium ferricyanide: a yellow precipitate is formed.

D: To 1 ml. of the solution prepared in *Identification test B* add 1 ml. of a saturated solution of potassium thiocyanate: a white, gelatinous precipitate is formed.

Melting range, page 814—Cetylpyridinium Chloride melts between 80° and 84°, the preliminary drying treatment being omitted.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Cetylpyridinium Chloride exhibits maxima only at the same wavelengths as that of NF Cetylpyridinium Chloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 8000 solution of Cetylpyridinium Chloride exhibits maxima and minima at the same wavelengths as that of NF Cetylpyridinium Chloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance occurring at about 259 mμ, do not differ by more than 3 percent.

Acidity—Dissolve 500 mg., accurately weighed, of Cetylpyridinium Chloride in 50 ml. of water, add phenolphthalein T.S., and titrate with 0.02 *N* sodium hydroxide: not more than 2.5 ml. is required for neutralization.

Water, page 900—Determine the water content of Cetylpyridinium Chloride by the titrimetric method: not less than 4.5 percent and not more than 5.5 percent is found.

Residue on ignition, page 858—Cetylpyridinium Chloride yields not more than 0.2 percent of residue on ignition, calculated on the anhydrous basis.

Heavy metals, *Method II*, page 806—The heavy metals limit for Cetylpyridinium Chloride is 20 parts per million.

Pyridine—Dissolve 1 g. of Cetylpyridinium Chloride in 10 ml. of sodium hydroxide solution (1 in 10) without heating: the odor of pyridine is not immediately perceptible.

Assay—Transfer about 200 mg., accurately weighed, of Cetylpyridinium Chloride to a glass-stoppered 250-ml. flask containing 75 ml. of water. Add 10 ml. of chloroform, 0.4 ml. of bromophenol blue solution (1 in 2000), and 5 ml. of a freshly prepared solution of sodium bicarbonate (4.2 in 1000), and titrate with 0.02 *M* sodium tetraphenylboron until the blue color disappears from the chloroform layer. Add the last portions of the sodium tetraphenylboron solution dropwise, agitating vigorously after each addition. Each ml. of 0.02 *M* sodium tetraphenylboron is equivalent to 6.800 mg. of $C_{21}H_{38}ClN$.

Packaging and storage—Preserve Cetylpyridinium Chloride in well-closed containers.

CATEGORY—Local anti-infective.

APPLICATION—Topically as a 1:100 to 1:1000 solution to intact skin; 1:1000 for minor lacerations; 1:2000 to 1:10,000 to mucous membranes.

Cetylpyridinium Chloride Solution

Cetylpyridinium Chloride Solution contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{21}H_{38}ClN . H_2O$.

Description—Cetylpyridinium Chloride Solution is a clear liquid. It is colorless unless a color has been added. It has an aromatic odor and a bitter taste.

Identification—

A: Evaporate a volume of Cetylpyridinium Chloride Solution, equivalent to about 500 mg. of cetylpyridinium chloride, on a steam bath to one-half its original volume: the resulting solution responds to *Identification tests B, C, and D* under *Cetylpyridinium Chloride*, page 144.

B: Dilute a volume of Cetylpyridinium Chloride Solution to a concentration equivalent to 125 mcg. of cetylpyridinium chloride in each ml.: the resulting solution exhibits ultraviolet absorption maxima and minima at the same wavelengths exhibited by a solution of NF Cetylpyridinium Chloride Reference Standard, similarly measured.

Assay—Pipet into a glass-stoppered 250-ml. flask a volume of Cetylpyridinium Chloride Solution, equivalent to about 150 mg. of cetylpyridinium chloride, and proceed as directed in the *Assay* under *Cetylpyridinium Chloride*, page 144, beginning with "Add 10 ml. of chloroform, ..." Each ml. of 0.02 *M* sodium tetraphenylboron is equivalent to 7.160 mg. of $C_{21}H_{38}ClN . H_2O$.

Packaging and storage—Preserve Cetylpyridinium Chloride Solution in tight containers.

Solution available—Cetylpyridinium Chloride Solution is usually available in the following concentration: 1:1000.

CATEGORY and APPLICATION—See Cetylpyridinium Chloride.

Chloral Betaine*

$$CCl_3CH(OH)_2 . (CH_3)_3\overset{+}{N}CH_2COO^-$$

Chloral Hydrate Betaine (1:1) Compound

$C_7H_{14}Cl_3NO_4$ Mol. wt. 282.55

Chloral Betaine is an adduct formed by the reaction of chloral hydrate with betaine. It contains not less than 56.0 percent and not more than 59.5 percent of $C_2H_3Cl_3O_2$ (chloral hydrate), and not less than 40.0 percent and not more than 44.0 percent of $C_5H_{11}NO_2$ (betaine).

Description—Chloral Betaine occurs as a white, crystalline powder having a bitter taste and a faint, penetrating and slightly acrid odor resembling that of chloral hydrate. When tested by the procedure for *Class Ia*, page 815, it melts at about 124° with decomposition.

Solubility—Chloral Betaine is very soluble in water. It is freely soluble in alcohol and is very slightly soluble in chloroform.

Identification—To about 250 mg. of Chloral Betaine add a few ml. of sodium hydroxide T.S.: chloroform, recognizable by its odor, is formed.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Chloral Betaine, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Chloral Betaine Reference Standard, similarly measured.

Water, page 900—Determine the water content of Chloral Betaine by the titrimetric method: not less than 5.9 percent and not more than 7.4 percent is found.

Residue on ignition, page 858—Chloral Betaine yields not more than 0.2 percent of residue on ignition.

Chloride—Dissolve 10.0 g. of Chloral Betaine in 50 ml. of water, add 10.0 ml. of 0.1 *N* silver nitrate, 3 ml. of nitric acid,

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* Patented. See notice, page ii.

5 ml. of nitrobenzene, and 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 3.545 mg. of Cl. Not more than 0.1 percent is found.

Heavy metals, *Method II*, page 806—The heavy metals limit for Chloral Betaine is 20 parts per million.

Chlorobenzenes—

Solvent hexane—Use pretested solvent hexane that has proven to give a distinct peak for each of the four chlorobenzenes, when tested with the USP Chlorobenzenes Reference Standard, and produces no detectable peaks at the retention times of the four chlorobenzenes when tested separately.

Procedure—Transfer 2.5 g. of Chloral Betaine, accurately weighed, to a 5-ml. volumetric flask, add water to volume, and mix. Pipet 0.5 ml. of *Solvent hexane* into the flask, shake for 2 minutes, and allow the layers to separate. Inject a 1-μl. portion of the hexane layer into a suitable gas chromatograph (see page 787). Preferably use an apparatus of the general type in which a stainless steel column about 3 to 4 meters in length and about 3 to 4 mm. in outside diameter is packed with 80- to 100-mesh chromatographic siliceous earth prepared for gas chromatography. Use as the liquid phase a suitable silicone fluid in 10 percent concentration. Use helium, flowing at the rate of 50 to 60 ml. per minute, as the carrier gas. Precondition the column at 200° to 205° for 36 hours. Maintain the injection port temperature at about 240° and the column temperature at about 120°. Preferably use a high-sensitivity detector. The operating conditions of the apparatus may vary, depending upon the particular instrument used, but a suitable chromatogram is one in which the resolution factor, *R*, is not less than 0.9 between the chlorobenzene peaks in the standard.

Similarly, carry 2.5 g. of USP Chlorobenzenes Reference Standard through the foregoing procedure. Each μl. of the hexane solution prepared contains 0.1 mcg. of monochlorobenzene and 0.05 mcg. each of *ortho-*, *meta-*, and *para*-dichlorobenzene. Identify the peaks corresponding to the four chlorobenzenes contained in the USP Chlorobenzenes Reference Standard, and measure the area under each peak.

Calculate the concentration, in parts per million, of each chlorobenzene in the Chloral Betaine by the formula $200C \times (A_U/A_S)$, in which C is the concentration, in mcg. per μl., of the corresponding chlorobenzene in the hexane solution prepared from USP Chlorobenzenes Reference Standard, and A_U and A_S are the areas under the curves for the sample and standard, respectively, for each chlorobenzene contained in the Reference Standard. The total chlorobenzene content of Chloral Betaine does not exceed 100 parts per million.

Assay for chloral hydrate—Dissolve about 500 mg. of Chloral Betaine, accurately weighed, in 25 ml. of water, add 25.0 ml. of 0.1 *N* sodium hydroxide, swirl to mix, and allow the mixture to stand for 2 minutes. Add 3 drops of phenolphthalein T.S., and titrate the excess sodium hydroxide at once with 0.1 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* sodium hydroxide is equivalent to 16.54 mg. of $C_2H_3Cl_3O_2$.

Assay for betaine—Dissolve about 200 mg. of Chloral Betaine, accurately weighed, in 50 ml. of glacial acetic acid, add 1.5 to 2 ml. of a 1 in 5000 solution of *p*-naphtholbenzein in glacial acetic acid, and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 11.72 mg. of $C_5H_{11}NO_2$.

Packaging and storage—Preserve Chloral Betaine in tight containers.

CATEGORY—Sedative.

USUAL DOSE—**870 mg.** to **1.74 g.** 15 to 30 minutes before bedtime.

Chloral Betaine Tablets

Chloral Betaine Tablets contain chloral betaine equivalent to not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_2H_3Cl_3O_2$ (chloral hydrate).

Identification—Remove any film coating from Chloral Betaine Tablets by cutting with a sharp knife or by shaking with chloroform for about 1 hour, and triturate the tablet to a fine powder: the infrared absorption spectrum of a potassium bromide dispersion prepared from the powder exhibits maxima only at the same wavelengths as that of NF Chloral Betaine Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Chloral Betaine Tablets, determined in simulated gastric fluid T.S. without the use of disks, is 15 minutes.

Weight variation, page 901—Chloral Betaine Tablets meet the requirements of the weight variation test for tablets.

Assay—Transfer 10 Chloral Betaine Tablets to a 200-ml. volumetric flask, add 160 ml. of water, and shake mechanically for about 45 minutes or until tablet disintegration is completed. Dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate. Transfer an accurately measured volume of the subsequent filtrate, equivalent to about 250 mg. of chloral betaine, to a 125-ml. conical flask, add 20.0 ml. of 0.1 *N* sodium hydroxide, and allow the mixture to stand for 2 minutes. Add 3 drops of phenolphthalein T.S., and titrate the excess sodium hydroxide with 0.1 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* sodium hydroxide is equivalent to 16.54 mg. of $C_2H_3Cl_3O_2$.

Packaging and storage—Preserve Chloral Betaine Tablets in tight, light-resistant containers.

Tablets available—Chloral Betaine Tablets usually available contain chloral betaine equivalent to the following amount of chloral hydrate: 500 mg.

CATEGORY and DOSE—See Chloral Betaine.

Sterile Chloramphenicol for Suspension

Sterile Chloramphenicol for Suspension is a sterile, dry mixture of chloramphenicol and suitable buffers, suspending agents, and preservatives. It contains not less than 85.0 percent of the labeled amount of $C_{11}H_{12}Cl_2N_2O_5$. Sterile Chloramphenicol for Suspension conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Sterile Chloramphenicol for Suspension is a white to grayish white or yellowish white, crystalline powder. It is odorless.

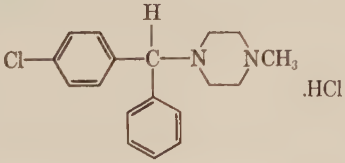
Packaging and storage—Preserve Sterile Chloramphenicol for Suspension in *Containers for Sterile Solids* as described under *Injections*, page 810.

Size available—Sterile Chloramphenicol for Suspension is usually available in the following amount: 1 g.

CATEGORY—Antibacterial; antirickettsial.

USUAL DOSE OF CHLORAMPHENICOL—Intramuscular, **1 g.** every 8 hours.

Chlorcyclizine Hydrochloride



1-(*p*-Chloro-α-phenylbenzyl)-4-methylpiperazine Monohydrochloride

$C_{18}H_{21}ClN_2.HCl$ Mol. wt. 337.30

Chlorcyclizine Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{18}H_{21}ClN_2.HCl$, calculated on the dried basis.

Description—Chlorcyclizine Hydrochloride occurs as a white crystalline powder, which is odorless or almost odorless.

Solubility—Chlorcyclizine Hydrochloride is freely soluble in water and in chloroform. It is soluble in alcohol and is practically insoluble in ether and in benzene.

Identification—

A: Dissolve 25 mg. of Chlorcyclizine Hydrochloride in 5 ml. of sulfuric acid: a brilliant yellow color is produced, which disappears upon dilution with 20 ml. of water, leaving a colorless solution.

B: Chlorcyclizine Hydrochloride responds to the tests for *Chloride*, page 808.

Melting range, *Class Ia*, page 815—Chlorcyclizine Hydrochloride melts between 222° and 227°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Chlorcyclizine Hydrochloride, previously dried at 120° for

3 hours, exhibits maxima only at the same wavelengths as that of NF Chlorcyclizine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 4000 solution of Chlorcyclizine Hydrochloride in 0.5 *N* sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Chlorcyclizine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 261 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Chlorcyclizine Hydrochloride (1 in 100) is between 4.8 and 5.5.

Loss on drying, page 814—Dry Chlorcyclizine Hydrochloride at 120° for 3 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Chlorcyclizine Hydrochloride yields not more than 0.2 percent of residue on ignition.

Assay—Dissolve about 500 mg. of Chlorcyclizine Hydrochloride, accurately weighed, in 80 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 16.86 mg. of $C_{18}H_{21}ClN_2.HCl$.

Packaging and storage—Preserve Chlorcyclizine Hydrochloride in tight, light-resistant containers.

CATEGORY—Antihistaminic.

USUAL DOSE—**50 mg.** up to four times a day.

USUAL DOSE RANGE—**25** to **100 mg.**

Chlorcyclizine Hydrochloride Tablets

Chlorcyclizine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{21}ClN_2.HCl$.

Identification—

A: Extract a quantity of finely powdered Chlorcyclizine Hydrochloride Tablets, equivalent to about 50 mg. of chlorcyclizine hydrochloride, with two 5-ml. portions of chloroform. Filter the combined chloroform solutions, and evaporate to dryness: the residue so obtained responds to *Identification test A* under *Chlorcyclizine Hydrochloride,* page 147.

B: Chlorcyclizine Hydrochloride Tablets meet the requirements under *Identification—Organic Nitrogenous Bases,* page 810.

Disintegration, page 858—The disintegration time limit for Chlorcyclizine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Chlorcyclizine Hydrochloride Tablets meet the requirements of the content uniformity test for Tablets.

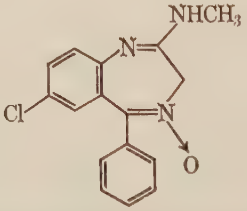
Assay—Proceed with Chlorcyclizine Hydrochloride Tablets as directed under *Salts of Organic Nitrogenous Bases,* page 865, diluting the *Standard Preparation* and the *Assay Preparation* with an equal volume of 0.5 *N* sulfuric acid, and determining the absorbance at 261 mμ. Calculate the quantity, in mg., of $C_{18}H_{21}ClN_2.HCl$ in the portion of the Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard Preparation.*

Packaging and storage—Preserve Chlorcyclizine Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Chlorcyclizine Hydrochloride Tablets usually available contain the following amounts of chlorcyclizine hydrochloride: 25 and 50 mg.

CATEGORY and DOSE—See Chlorcyclizine Hydrochloride.

Chlordiazepoxide*



7-Chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide

$C_{16}H_{14}ClN_3O$ Mol. wt. 299.76

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* Patented. See notice, page ii.

Chlordiazepoxide contains not less than 99.0 percent and not more than 101.0 percent of $C_{16}H_{14}ClN_3O$, calculated on the dried basis.

Description—Chlordiazepoxide occurs as a yellow, practically odorless, crystalline powder. It is sensitive to sunlight.

Solubility—Chlordiazepoxide is sparingly soluble in chloroform and in alcohol. It is insoluble in water.

Identification—To about 20 mg. of Chlordiazepoxide, add 5 ml. of hydrochloric acid and 10 ml. of water, and heat to boiling to effect hydrolysis. To the cooled solution add 2 ml. of sodium nitrite solution (1 in 1000), shake, add 1 ml. of ammonium sulfamate solution (1 in 200), then shake for 2 minutes and add 1 ml. of *N*-1-naphthylethylenediamine dihydrochloride solution (1 in 1000): a reddish violet color is produced.

Melting range, page 814—Chlordiazepoxide melts between 240° and 244°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Chlordiazepoxide, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Chlordiazepoxide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—[Note: Use low-actinic glassware.] The ultraviolet absorption spectrum of a 1 in 200,000 solution of Chlordiazepoxide in 0.1 *N* alcoholic sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Chlordiazepoxide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 245 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Chlordiazepoxide at 105° for 3 hours: it loses not more than 0.3 percent of its weight.

Residue on ignition, page 858—Chlordiazepoxide yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Chlordiazepoxide is 20 parts per million.

Limit of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide and 2-amino-5-chlorobenzophenone—Transfer 50.0 mg. of Chlordiazepoxide to a 10-ml. conical flask, add 2.5 ml. of acetone, and shake. Allow any undissolved particles to settle, and apply 50 μl. of the supernatant solution to a suitable thin-layer chromatographic plate (see page 791) coated with a 0.25-mm. layer of silica gel G. Apply to the same plate 10 μl. of an acetone solution containing 100 mcg. per ml. of NF 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide Reference Standard, and 10 μl. of an acetone solution containing 10 mcg. per ml. of NF 2-Amino-5-chlorobenzophenone Reference Standard. Develop the chromatogram in an unsaturated chamber with ethyl acetate until the solvent front has moved at least 10 cm. from the origin. Remove the plate from the developing chamber, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with diluted sulfuric acid, followed by drying at 105° for 15 minutes, and then spraying in succession with sodium nitrite solution (1 in 1000), ammonium sulfamate solution (1 in 200), and *N*-1-naphthylethylenediamine dihydrochloride solution (1 in 1000). Any spots from the sample solution are not greater in size or intensity than the spots, occurring at the respective R_f values, produced by the Reference Standard solutions, corresponding to not more than 0.1 percent of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide, and not more than 0.01 percent of 2-amino-5-chlorobenzophenone.

Assay—Dissolve about 800 mg. of Chlordiazepoxide, accurately weighed, in 90 ml. of chloroform, add 3 drops of methyl red T.S., and titrate with 0.1 *N* perchloric acid in dioxane to a pink end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 29.98 mg. of $C_{16}H_{14}ClN_3O$.

Packaging and storage—Preserve Chlordiazepoxide in tight, light-resistant containers.

Category—Tranquilizer (minor).

Usual dose—**5** or **10 mg.** three or four times a day.

Usual dose range—**5** to **25 mg.**

Chlordiazepoxide Tablets

Chlordiazepoxide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{14}ClN_3O$.

Identification—A portion of finely powdered Chlordiazepoxide Tablets, equivalent to about 20 mg. of chlordiazepoxide, responds to the *Identification test* under *Chlordiazepoxide*, page 148.

Ultraviolet absorption, page 866—The

solution of chlordiazepoxide employed for measurement of absorbance in the *Assay*, when diluted 1:1 with 0.1 *N* alcoholic sulfuric acid, exhibits maxima at the same wavelengths as the NF Chlordiazepoxide Reference Standard solution prepared for the *Assay*, and similarly diluted, and the ratio A_{245}/A_{311} is between 2.90 and 3.45.

Disintegration, page 878—The disintegration time limit for Chlordiazepoxide Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—[Note: Use low-actinic glassware.] Chlordiazepoxide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Crush one tablet in a suitable container, add 5 ml. of dimethylformamide, and let stand for about 20 to 30 minutes. Dilute this solution quantitatively and stepwise, if necessary, with 0.1 *N* sulfuric acid, filtering prior to final dilution, to provide a solution containing approximately 15 mcg. of chlordiazepoxide per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Chlordiazepoxide Reference Standard, in the same medium at a concentration of about 15 mcg. per ml., in 1-cm. cells, at the maximum at about 309 mμ, with a suitable spectrophotometer, using 0.1 *N* sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{14}ClN_3O$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of chlordiazepoxide, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of chlordiazepoxide in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Limit of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide and 2-amino-5-chlorobenzophenone—Transfer an accurately weighed portion of finely powdered Chlordiazepoxide Tablets, equivalent to about 25.0 mg. of chlordiazepoxide, to a 10-ml. conical flask, add 2.5 ml. of acetone, and shake. Allow the excipients to settle, and apply 50 μl. of the supernatant solution to a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G. Apply to the same plate 20 μl. of an acetone solution containing 1 mg. per ml. of NF 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide Reference Standard, and 5 μl. of an acetone solution containing 100 mcg. per ml. of NF 2-Amino-5-chlorobenzophenone Reference Standard. Develop the chromatogram in an unsaturated chamber with ethyl acetate until the solvent front has moved at least 10 cm. from the origin. Remove the plate from the developing chamber, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with diluted sulfuric acid, followed by drying at 105° for 15 minutes, and then spraying in succession with sodium nitrite solution (1 in 1000), ammonium sulfamate solution (1 in 200), and *N*-1-naphthylethylenediamine dihydrochloride solution (1 in 1000). Any spots from the sample solution are not greater in size or intensity than the spots, occurring at the respective R_f values, produced by the Reference Standard solutions, corresponding to not more than 4 percent of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide, and not more than 0.1 percent of 2-amino-5-chlorobenzophenone.

Assay—[Note: Use low-actinic glassware.] Weigh and finely powder not less than 20 Chlordiazepoxide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 30 mg. of chlordiazepoxide, to a glass-stoppered centrifuge tube, and add 40 ml. of chloroform. Shake the mixture for 20 minutes in a mechanical shaker, then centrifuge. Transfer the chloroform extract to a 200-ml. volumetric flask. Repeat the extraction procedure three more times with 40-ml. portions of chloroform, combining the extracts in the volumetric flask, and dilute to volume with chloroform. Transfer this solution to a 250-ml. separator, and add 25 ml. of pH 9.7 borate buffer solution. (Prepare the buffer by mixing 30 ml. of 0.1 *N* sodium hydroxide with 70 ml. of a solution made with 12.4 g. of boric acid dissolved in 100 ml. of 1 *N* sodium hydroxide and diluted to 1000 ml. with water.) Shake well, and pass the chloroform layer through a funnel containing a pledget of glass wool layered with anhydrous sodium sulfate. Pipet 10.0 ml. of the filtrate into a 100-ml. volumetric flask, and evaporate to dryness under a stream of nitrogen. Using 0.1 *N* alcoholic sulfuric acid, dissolve the residue, dilute to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Chlordiazepoxide Reference Standard, in the same medium, at a concentration of about 15 mcg. per ml., in 1-cm. cells, at the maximum at about 311 mμ, with a suitable spectrophotometer, using 0.1 *N* alcoholic sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{14}ClN_3O$ in the portion of the tablets taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

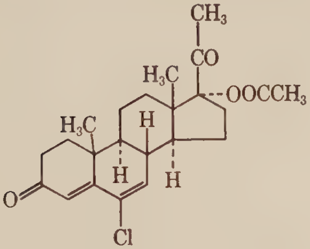
Packaging and storage—Preserve Chlordiazepoxide Tablets in tight, light-resistant containers.

Tablets available—Chlordiazepoxide

Tablets usually available contain the following amounts of chlordiazepoxide: 5, 10, and 25 mg.

Category and Dose—See Chlordiazepoxide.

Chlormadinone Acetate*



6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione Acetate

$C_{23}H_{29}ClO_4$ Mol. wt. 404.94

Chlormadinone Acetate contains not less than 97.0 percent and not more than 102.0 percent of $C_{23}H_{29}ClO_4$, calculated on the dried basis.

Description—Chlormadinone Acetate occurs as an off-white to pale yellow, fluffy, crystalline powder. It is odorless.

Solubility—Chlormadinone Acetate is freely soluble in chloroform, and is slightly soluble in ether, in alcohol and in methanol. It is practically insoluble in water.

Identification—

A: Prepare a solution of Chlormadinone Acetate in chloroform containing 10 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a chloroform solution of NF Chlormadinone Acetate Reference Standard containing 10 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and ether (9:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Observe first under shortwave ultraviolet light and then under longwave ultraviolet light. Spray the plate with a 1 in 10 solution of phosphomolybdic acid in methanol, and then heat the plate on a steam bath over a thin metal sheet for 5 minutes. The R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

B: To about 50 mg. of Chlormadinone Acetate contained in a test tube, add 2 ml. of alcohol and 2 ml. of dilute sulfuric acid (1 in 3.5), and boil gently for about 1 minute: the odor of ethyl acetate is perceptible.

Melting range, *Class Ia,* page 815—Chlormadinone Acetate melts within a range of 4° between 206° and 214°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Chlormadinone Acetate, previously dried in vacuum at 40° for 16 hours, exhibits maxima only at the same wavelengths as that of NF Chlormadinone Acetate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Chlormadinone Acetate in methanol exhibits maxima and minima at the same wavelengths as that of NF Chlormadinone Acetate Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Chlormadinone Acetate, previously dried in vacuum at 40° for 16 hours, determined in a solution in chloroform containing 200 mg. of Chlormadinone Acetate in each 10 ml., is between 0° and −6°.

X-ray diffraction, page 902—The X-ray diffraction pattern of Chlormadinone Acetate conforms to the following pattern:

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* Patented. See notice, page ii.

d	I/I_1
9.77	50
8.19	5
7.29	5
6.54	100
6.08	5
5.73	75
5.48	15
5.21	5
5.02	15
4.78	25
4.51	15
4.25	25
4.07	5
3.93	3
3.83	3
3.65	50
3.42	20
3.21	10
3.08	10
2.91	3
2.76	3
2.65	3
2.55	3b
2.38	3
2.29	3
2.24	3
2.19	3
2.13	3
2.08	3
2.01	3
1.96	3

Loss on drying, page 814—Dry Chlormadinone Acetate at 105° for 3 hours: it loses not more than 1 percent of its weight.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Chlormadinone Acetate Reference Standard to prepare a solution in chloroform containing approximately 10 mg. per ml.

Test preparation—Weigh accurately about 50 mg. of Chlormadinone Acetate, previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of chloroform to make 5.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, applying 10 μl. each of the *Test Preparation* and of the *Standard Preparation* to the chromatographic plate and using a solvent system consisting of chloroform and ether (70:30). (Note: Use chloroform, rather than alcohol, to elute the silica gel bands). Determine the absorbances at the maximum at about 284 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 5 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Chlormadinone Acetate taken: not more than 3 percent is found.

Assay—Transfer about 80 mg. of Chlormadinone Acetate, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 1.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Chlormadinone Acetate Reference Standard, in the same medium at a concentration of about 8 mcg. per ml., in 1-cm. cells, at the maximum at about 284 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{23}H_{29}ClO_4$ in the Chlormadinone Acetate taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Chlormadinone Acetate in tight, light-resistant containers.

CATEGORY—Progestin.

USUAL DOSE—See Chlormadinone Acetate and Mestranol Tablets.

Chlormadinone Acetate and Mestranol Tablets

Chlormadinone Acetate and Mestranol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_{23}H_{29}ClO_4$ (chlormadinone acetate) and of $C_{21}H_{26}O_2$ (mestranol).

Identification—

A: The solution prepared for measurement of absorbance in the *Assay for chlormadinone acetate* exhibits a maximum at 285 ± 3 mμ.

B: The solution prepared for measurement of absorbance in the *Assay for mestranol* exhibits a maximum at 545 ± 3 mμ.

Disintegration, page 878—The disintegration time limit for Chlormadinone Acetate and Mestranol Tablets is 30 minutes.

Content uniformity, *Method II,* page 799

—Chlormadinone Acetate and Mestranol Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure:

Chlormadinone acetate standard preparation—Transfer about 10 mg. of NF Chlormadinone Acetate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add chloroform to volume, and mix.

Mestranol standard preparation—Transfer about 8 mg. of USP Mestranol Reference Standard, accurately weighed, to a 200-ml. volumetric flask, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Test preparation—Transfer a tablet to a 60-ml. separator containing 5 ml. of water and 0.05 ml. of sodium hydroxide solution (1 in 2). Carefully pipet 20.0 ml. of chloroform into the separator, stopper the separator with a stopper moistened with water, shake until the tablet has completely disintegrated, and then shake for 3 minutes longer. Allow the layers to separate, and collect the chloroform layer in a 25-ml. glass-stoppered flask containing 3 g. of anhydrous sodium sulfate.

Procedure for chlormadinone acetate—Transfer an accurately measured volume of the *Test preparation*, equivalent to about 200 mcg. of chlormadinone acetate, to a 25-ml. volumetric flask, and transfer 2.0 ml. of the *Chlormadinone acetate standard preparation* to a second 25-ml. volumetric flask. Dilute each flask to volume with chloroform, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 285 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{23}H_{29}ClO_4$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of chlormadinone acetate, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of chlormadinone acetate in the final sample solution, based upon the labeled quantity and the extent of dilution; C is the exact concentration, in mcg. per ml., of the diluted *Chlormadinone acetate standard solution;* A_U is the absorbance of the final sample solution; and A_S is the absorbance of the diluted *Chlormadinone acetate standard solution.*

Procedure for mestranol—Transfer an accurately measured volume of the *Test preparation*, equivalent to about 16 mcg. of mestranol, to a 25-ml. volumetric flask, and transfer 4.0 ml. of *Mestranol standard preparation* to a second 25-ml. volumetric flask. Wash down the neck of each flask with 2 ml. of chloroform, and then evaporate the contents of each flask to dryness at room temperature with the aid of a stream of air, without heating. Pipet 0.3 ml. of methanol into each flask, and dissolve the residues completely by rotating the flasks. Immerse the bulb and part of the neck of each flask in a constant-temperature water bath maintained at 25°, and, with constant swirling, add 10.0 ml. of *Color reagent*, prepared as directed in the *Assay for mestranol*, to each flask. Mix, and after 6 ± 1 minutes from the time of addition of the *Color reagent*, determine the absorbance of each solution in a 1-cm. cell, at the maximum at about 545 mμ, with a suitable spectrophotometer, using the *Color reagent* as the blank. Record the absorbance of the solution from the *Mestranol standard preparation* as A_S and that from the *Test preparation* as A_U. Calculate the quantity, in mcg., of $C_{21}H_{26}O_2$ in the tablet by the formula $(T/DV) \times 4C \times (A_U/A_S)$, in which T is the labeled quantity of mestranol, in mcg., in the tablet; D is the exact concentration, in mcg. per ml., of mestranol in the *Test preparation*, based upon the labeled quantity of mestranol per tablet; V is the volume, in ml., of the *Test preparation* taken; and C is the exact concentration, in mcg. per ml., of the *Mestranol standard preparation.*

Assay for chlormadinone acetate—Weigh not less than 20 Chlormadinone Acetate and Mestranol Tablets, and transfer a number of the tablets, equivalent to about 40 mg. of chlormadinone acetate, to a 125-ml. separator containing 30 ml. of water, 0.15 ml. of sodium hydroxide solution (1 in 2), and 40 ml. of chloroform. Shake until complete disintegration is effected. Allow the layers to separate, and drain the chloroform layer through a sintered-glass filter funnel containing 10 g. of anhydrous sodium sulfate, collecting the filtrate in a 200-ml. volumetric flask. Extract with three additional 40-ml. portions of chloroform, passing each extract through the funnel into the flask. Rinse the filter with chloroform, collecting the filtrate in the flask, dilute to volume with chloroform, and mix. Transfer 2.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Chlormadinone Acetate Reference Standard, in the same medium at a concentration of about 8 mcg. per ml., in 1-cm. cells, at the maximum at about 285 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{23}H_{29}ClO_4$ in the Tablets taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Assay for mestranol—

Color reagent—Transfer 30.0 ml. of methanol to a 100-ml. volumetric flask, and place the flask in an ice-water bath maintained below 15°. With constant stirring, slowly and cautiously add sulfuric acid until a volume of about 95 ml. is reached. Allow the solution to return to room temperature, dilute to volume with sulfuric acid, and mix.

Standard preparation—Transfer about 16 mg. of USP Mestranol Reference Standard, accurately weighed, to a 200-ml. volumetric flask, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparation—Weigh not less than 20 Chlormadinone Acetate and Mestranol Tablets, and transfer a number of tablets, equivalent to about 1.6 mg. of mestranol, to a 125-ml. separator containing 30 ml. of water, 0.15 ml. of sodium hydroxide solution (1 in 2), and 40 ml. of chloroform. Shake until complete disintegration is effected. Allow the layers to separate, and drain the chloroform layer through a sintered-glass filter funnel containing 10 g. of anhydrous sodium sulfate, collecting the filtrate in a 200-ml. volumetric flask. Extract with three additional 40-ml. portions of chloroform, passing each extract through the funnel into the flask. Rinse the filter with chloroform, collecting the filtrate in the flask, dilute to volume with chloroform, and mix.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate 25-ml. volumetric flasks, and wash down the neck of each flask with 2 ml. of chloroform. Carefully evaporate the contents of each flask to dryness at room temperature with the aid of a stream of air, without heating. Pipet 0.3 ml. of methanol into each flask, and dissolve the residues completely by rotating the flasks. Immerse the bulb and part of the neck of each flask in a constant-temperature water bath maintained at 25°, and, with constant stirring, add 10.0 ml. of *Color reagent* to each flask. Mix, and after 6 ± 1 minutes from the time of the addition of the *Color reagent*, determine the absorbance of each solution in a 1-cm. cell, at the maximum at about 545 mμ, with a suitable spectrophotometer, using the *Color reagent* as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{26}O_2$ in the Tablets taken by the formula $0.2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

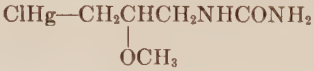
Packaging and storage—Preserve Chlormadinone Acetate and Mestranol Tablets in well-closed containers.

Tablets available—Chlormadinone Acetate and Mestranol Tablets usually available contain the following amount of chlormadinone acetate: 2 mg.; and of mestranol: 80 mcg.

Category—Estrogen-progestin (ovulation control).

Usual dose—Beginning on day 5 of menstrual cycle, 80 mcg. of mestranol daily for 15 days, then 80 mcg. of mestranol and 2 mg. of chlormadinone acetate daily for 5 days.

Chlormerodrin*



$$ClHg{-}CH_2\underset{\displaystyle OCH_3}{CH}CH_2NHCONH_2$$

Chloro(2-methoxy-3-ureidopropyl)mercury

$C_5H_{11}ClHgN_2O_2$ Mol. wt. 367.20

Chlormerodrin contains not less than 98.8 percent and not more than 100.7 percent of $C_5H_{11}ClHgN_2O_2$, calculated on the dried basis.

Description—Chlormerodrin occurs as a white, odorless, bitter powder.

Solubility—Chlormerodrin is sparingly soluble in water, and is slightly soluble in methanol and in absolute alcohol. It is practically insoluble in acetone and in ether.

Identification—Mix 50 mg. of Chlormerodrin with 3 drops of water, dip a clean copper wire in the paste and hold it in the nonluminous portion of the flame of a Bunsen burner: the flame turns green (*presence of chlorine*).

Melting range, page 814—Chlormerodrin melts between 145° and 155°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Chlormerodrin, previously dried at 105° for 5 hours, exhibits maxima only at the same wavelengths as that of NF Chlormerodrin Reference Standard, similarly measured.

Clarity and color of solution—Dissolve

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* Patented. See notice, page ii.

1 g. of Chlormerodrin in 60 ml. of approximately 0.05 *N* sodium hydroxide: the solution is colorless and exhibits not more than a faint opalescence.

Loss on drying, page 814—Dry Chlormerodrin at 105° for 5 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Chlormerodrin yields not more than 0.3 percent of residue on ignition.

Mercury ions—Suspend 500 mg. of Chlormerodrin in 5 ml. of water, and dissolve as completely as possible by the gradual, and finally dropwise, addition, with stirring, of approximately 14 ml. of 0.1 *N* sodium hydroxide. Transfer the solution to a 25-ml. volumetric flask, dilute to volume with water, mix, filter, and add 4 drops of sodium sulfide T.S. to 5 ml. of the filtrate: not more than a faint coloration of the solution is noticeable within 20 seconds.

Assay—Transfer about 400 mg. of Chlormerodrin, accurately weighed, to a 400-ml. beaker, add 5 ml. of hydrochloric acid and 150 ml. of water, heat on a steam bath for about 5 minutes, and, while still on the steam bath, pass hydrogen sulfide into the solution for about 5 minutes. Transfer the precipitate quantitatively to a tared sintered-glass crucible, wash the precipitate successively with portions of water, alcohol, carbon disulfide, and alcohol, allowing the liquid to run through the filter without suction, and finally wash with ether. Dry the crucible and contents at 105° for 2 hours. The weight of mercuric sulfide so obtained, multiplied by 1.578, represents the weight of $C_5H_{11}ClHgN_2O_2$ in the portion of Chlormerodrin taken.

Packaging and storage—Preserve Chlormerodrin in well-closed containers.

CATEGORY—Diuretic.

USUAL DOSE RANGE—**55** to **110 mg.** daily.

Chlormerodrin Tablets

Chlormerodrin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_5H_{11}ClHgN_2O_2$.

Identification—

A: A portion of powdered Chlormerodrin Tablets, equivalent to about 50 mg. of chlormerodrin, responds to the *Identification test* under *Chlormerodrin,* page 154.

B: The black precipitate obtained in the *Assay* is insoluble in hot 2 *M* nitric acid.

Disintegration, page 878—The disintegration time limit for Chlormerodrin Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Chlormerodrin Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 25-ml. volumetric flask, using about 20 ml. of pH 10.0 borate buffer solution (prepared by dissolving 21.64 g. of boric acid and 235 g. of potassium chloride in 2000 ml. of water, adding 300 ml. of 1 *N* sodium hydroxide, and diluting to 7000 ml. with water) to effect the transfer. Warm on a steam bath for 20 minutes with occasional swirling, and cool. To the flask add 2 ml. of freshly prepared sodium bisulfite solution (1 in 40), dilute to volume with the buffer solution, mix, and filter, discarding the first 10 ml. of filtrate. Transfer a portion of the subsequent filtrate to a polarographic cell, insert the dropping mercury electrode of a suitable polarograph (see page 847), and record the polarogram from -0.1 volt to -0.9 volt, using a saturated calomel electrode as the reference electrode. Determine the height of the diffusion current $[(i_d)_U]$ as the difference between the residual current and the diffusion current plateau. Concomitantly and similarly determine the diffusion current $[(i_d)_S]$ of a solution containing about 366 mcg. of NF Chlormerodrin Reference Standard in each ml. and prepared as directed for the sample solution. Calculate the quantity, in mg., of $C_5H_{11}ClHgN_2O_2$ in the tablet by the formula $(T/D) \times C \times [(i_d)_U/(i_d)_S]$, in which T is the labeled quantity of chlormerodrin, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of the sample solution based upon the labeled quantity per tablet and the extent of dilution, and C is the exact concentration, in mcg. per ml., of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Chlormerodrin Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 250 mg. of chlormerodrin, to a 250-ml. volumetric flask, add 15 ml. of hydrochloric acid and 150 ml. of water, shake the mixture in a mechanical shaker for 1 hour, dilute to volume with water, mix, and filter. Transfer an accurately measured portion of the filtrate, equivalent to about 200 mg. of chlormerodrin, to a suitable beaker, and proceed as directed in the *Assay* under *Chlormerodrin,* page 154, beginning with "... heat on a steam bath...." The weight of mercuric sulfide, multiplied by

1.578, represents the weight of $C_5H_{11}ClHgN_2O_2$ in the portion of the Tablets taken.

Packaging and storage—Preserve Chlormerodrin Tablets in well-closed containers.

Tablets available—Chlormerodrin Tablets usually available contain the following amount of chlormerodrin: 18.3 mg.

CATEGORY AND DOSE—See Chlormerodrin.

Chloroform

$CHCl_3$ Mol. wt. 119.38

Chloroform contains not less than 99.0 percent and not more than 99.5 percent of $CHCl_3$, the remainder consisting of alcohol.

Caution: Care should be taken not to vaporize Chloroform in the presence of a flame, because of the production of harmful gases.

Description—Chloroform is a clear, colorless, mobile liquid, having a characteristic, ethereal odor, and a burning, sweet taste. It is not flammable, but its heated vapor burns with a green flame. It boils at about 61°. It is affected by light.

Solubility—Chloroform is slightly soluble in water. It is miscible with alcohol, with ether, with benzene, with solvent hexane, and with fixed and volatile oils.

Specific gravity, page 866—The specific gravity of Chloroform is not less than 1.474 and not more than 1.478, indicating not less than 99.0 percent and not more than 99.5 percent of $CHCl_3$.

Nonvolatile residue—Evaporate 50 ml. of Chloroform in a platinum or porcelain dish on a steam bath, and dry at 105° for 1 hour: the weight of the residue does not exceed 1 mg. (20 parts per million, w/v).

Chloride and free chlorine—Shake 10 ml. of Chloroform with 25 ml. of oxygen- and carbon dioxide-free water, and allow the liquids to separate completely: separate portions of 10 ml. each of the water layer are not affected by a few drops of silver nitrate T.S. (*chloride*), or colored blue by the addition of a few drops each of potassium iodide T.S. and starch T.S. (*free chlorine*).

Readily carbonizable substances—Transfer 40 ml. of Chloroform to a glass-stoppered cylinder previously rinsed with sulfuric acid T.S. and allowed to drain for 10 minutes. Add 5 ml. of sulfuric acid T.S., and shake the mixture vigorously for 5 minutes. Allow the liquids to separate completely: the Chloroform remains colorless and the acid has no more color than Matching Fluid A (see page 856).

Odorous and chlorinated decomposition products—Dilute 2 ml. of the sulfuric acid separated from the Chloroform in the test for *Readily carbonizable substances* with 5 ml. of water: the liquid is colorless and clear, and while hot from the mixing emits but a faint vinous or ether odor (*odorous decomposition products*). When further diluted with 10 ml. of water, it remains clear, and is not affected within 1 minute by the addition of 3 drops of silver nitrate T.S. (*chlorinated decomposition products*).

Acid and phosgene—Into each of two glass-stoppered 50-ml. color-comparison cylinders having an internal diameter of 20 mm., place 10 ml. of water, 2 drops of phenolphthalein T.S., and enough 0.01 *N* sodium hydroxide to produce, after vigorous shaking, pink tints of equal intensity. Into one of the cylinders measure 20.0 ml. of Chloroform, and again shake the mixture well. Add 0.01 *N* sodium hydroxide, dropwise from a buret, shaking the mixture well after each addition, until the pink color is reproduced in an intensity equal to that in the cylinder without the Chloroform. Not more than 0.20 ml. of 0.01 *N* sodium hydroxide is required to produce a pink color which persists for 15 minutes.

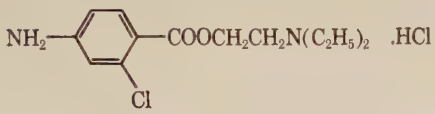
Aldehyde and ketone—Shake 3 ml. of Chloroform with 10 ml. of ammonia-free water in a glass-stoppered cylinder for 5 minutes. After the liquids separate, transfer 5 ml. of the water extract to another glass-stoppered cylinder containing 40 ml. of ammonia-free water, and add 5 ml. of alkaline mercuric-potassium iodide T.S.: no turbidity or precipitate develops within 1 minute.

Foreign odor—Pour 20 ml. of Chloroform, in small portions, upon a piece of clean, odorless filter paper laid flat upon a warmed glass plate, and rock the plate from side to side until the liquid is completely evaporated: no foreign odor becomes perceptible as the last portions of liquid disappear from the paper, and the paper remains odorless.

Packaging and storage—Preserve Chloroform in tight, light-resistant containers, preferably at a temperature not above 30°.

CATEGORY—Solvent.

Chloroprocaine Hydrochloride



2-(Diethylamino)ethyl 4-amino-2-chlorobenzoate Monohydrochloride

$C_{13}H_{19}ClN_2O_2 . HCl$ Mol. wt. 307.22

Chloroprocaine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{13}H_{19}ClN_2O_2 . HCl$, calculated on the dried basis.

Description—Chloroprocaine Hydrochloride occurs as a white, crystalline powder. Is odorless and is stable in air. Its solutions are acid to litmus. It exhibits local anesthetic properties when placed on the tongue.

Solubility—Chloroprocaine Hydrochloride is soluble in water and is slightly soluble in alcohol. It is very slightly soluble in chloroform and is practically insoluble in ether.

Identification—Chloroprocaine Hydrochloride responds to the tests for *Chloride*, page 808.

Melting range, page 814—Chloroprocaine Hydrochloride melts between 173° and 176°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Chloroprocaine Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Chloroprocaine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Chloroprocaine Hydrochloride in pH 4.5 buffer solution (prepared by dissolving 13.61 g. of monobasic potassium phosphate in 750 ml. of water, adjusting the pH to 4.5 ± 0.1 with 0.1 N potassium hydroxide, and diluting to 1000 ml. with water) exhibits maxima and minima at the same wavelengths as that of NF Chloroprocaine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 278 mμ, do not differ by more than 3 percent.

Acidity—Dissolve 1 g. of Chloroprocaine Hydrochloride in 25 ml. of water, add 2 drops of methyl red T.S., and titrate with 0.02 N sodium hydroxide: not more than 1.8 ml. is required to produce a yellow color.

Loss on drying, page 814—Dry about 500 mg. of Chloroprocaine Hydrochloride, accurately weighed, at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Chloroprocaine Hydrochloride yields not more than 0.15 percent of residue on ignition.

4-Amino-2-chlorobenzoic acid—

Standard preparation—Transfer 50.0 mg. of 4-amino-2-chlorobenzoic acid to a 100-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with water, and mix.

Test preparation—Transfer 100.0 mg. of Chloroprocaine Hydrochloride to a 25-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix.

Procedure—Transfer to separate separators 1.0 ml. each of the *Standard preparation* and of the *Test preparation*. To each separator add 1 ml. of 0.1 N hydrochloric acid, 1 ml. of water, and 2 ml. of sodium nitrite solution (1 in 1000), mix, and allow to stand for 3 minutes. Add 2 ml. of ammonium sulfamate solution (1 in 200), mix, and allow to stand for 2 minutes. Add 5 ml. of N-1-naphthylethylenediamine dihydrochloride solution (1 in 1000), mix, and allow to stand for 10 minutes. Add 7 ml. of chloroform, shake vigorously for 30 seconds, and add rapidly 0.8 ml. of sodium hydroxide solution (35 in 100) with continuous agitation. Shake immediately for 2 minutes, and allow the layers to separate. Remove most of the chloroform, and repeat the extraction with 5-ml. portions of chloroform until the chloroform phase remains colorless. Allow the aqueous layer to stand until clear: the color of the solution from the *Test preparation* is not more intense than that of the solution from the *Standard preparation* (0.625 percent).

Assay—Transfer about 400 mg. of Chloroprocaine Hydrochloride, accurately weighed, to a 200-ml. beaker, add 80 ml. of glacial acetic acid and 2 ml. of acetic anhydride, and heat on a steam bath for 10 minutes. Cool, add 10 ml. of mercuric acetate T.S., and titrate with 0.1 N perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N perchloric acid is equivalent to 30.72 mg. of $C_{13}H_{19}ClN_2O_2 . HCl$.

Packaging and storage—Preserve

Chloroprocaine Hydrochloride in well-closed containers.

Category—Local anesthetic.

Usual dose—Infiltration, **100 ml.** of 0.5 percent solution. Peripheral nerve block, **50 ml.** of 1 percent solution.

Usual dose range—Up to **1 g.** as a 0.5 to 3 percent solution.

Chloroprocaine Hydrochloride Injection

Chloroprocaine Hydrochloride Injection is a sterile solution of chloroprocaine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{19}ClN_2O_2.HCl$.

Identification—Chloroprocaine Hydrochloride Injection responds to the *Identification test* under *Chloroprocaine Hydrochloride*, page 157.

pH, page 824—The pH of Chloroprocaine Hydrochloride Injection is between 2.7 and 4.0.

4-Amino-2-chlorobenzoic acid—

Standard preparation—Prepare as directed in the test for *4-Amino-2-chlorobenzoic acid* under *Chloroprocaine Hydrochloride*, page 157.

Test preparation—Transfer to a 25-ml. volumetric flask an accurately measured volume of Chloroprocaine Hydrochloride Injection, equivalent to about 100 mg. of chloroprocaine hydrochloride, dilute to volume with water, and mix.

Procedure—Transfer to a separator 1.6 ml. of the *Standard preparation*, transfer to another separator 1.0 ml. of the *Test preparation*, and continue as directed for *Procedure* in the test for *4-Amino-2-chlorobenzoic acid* under *Chloroprocaine Hydrochloride*, page 157: the color of the solution from the *Test preparation* is not more intense than that from the *Standard preparation* (1 percent).

Other requirements—Chloroprocaine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—

Standard preparation—Transfer to a 125-ml. separator about 50 mg. of NF Chloroprocaine Hydrochloride Reference Standard, accurately weighed, add 20 ml. of water, and mix.

Assay preparation—Transfer to a 125-ml. separator an accurately measured volume of Chloroprocaine Hydrochloride Injection, equivalent to about 50 mg. of chloroprocaine hydrochloride, and dilute to about 20 ml. with water.

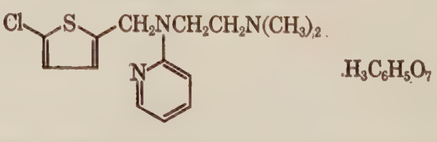
Procedure—To the *Standard preparation* and also to the *Assay preparation* add 5 ml. of ammonia T.S., then treat each as follows: Extract with five 25-ml. portions of chloroform, and filter the combined extracts through about 1 g. of anhydrous sodium sulfate supported on a pledget of glass wool. Collect the filtrate in a 200-ml. volumetric flask, add chloroform to volume, and mix. Transfer 3.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbances of both solutions at the maximum at about 278 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{13}H_{19}ClN_2O_2.HCl$ in each ml. of the Injection taken by the formula $(W/V) \times (A_U/A_S)$, in which W is the weight, in mg., of NF Chloroprocaine Hydrochloride Reference Standard used in preparing the *Standard preparation*, V is the volume, in ml., of the Injection taken, A_U is the absorbance of the solution from the *Assay preparation*, and A_S is the absorbance of the solution from the *Standard preparation*.

Packaging and storage—Preserve Chloroprocaine Hydrochloride Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injections available—Chloroprocaine Hydrochloride Injections usually available contain the following amounts of chloroprocaine hydrochloride: 300 and 600 mg. in 30 ml.

Category and Dose—See Chloroprocaine Hydrochloride.

Chlorothen Citrate



2-[(5-Chloro-2-thenyl)[2-(dimethylamino)ethyl]amino]pyridine Citrate (1:1)

$C_{14}H_{18}ClN_3S.C_6H_8O_7$ Mol. wt. 487.96

Chlorothen Citrate, dried in vacuum over phosphorus pentoxide for 5 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{14}H_{18}ClN_3S \cdot C_6H_8O_7$.

Description—Chlorothen Citrate occurs as a white, crystalline powder, usually having a faint odor. Its solutions are acid to litmus.

Solubility—Chlorothen Citrate is sparingly soluble in water. It is slightly soluble in alcohol, and practically insoluble in chloroform, in ether, and in benzene.

Identification—

A: Dissolve 25 mg. of Chlorothen Citrate in 5 ml. of sulfuric acid: a dark red color is produced, which disappears on dilution with 20 ml. of water with formation of a brown precipitate.

B: Dissolve about 500 mg. of Chlorothen Citrate in 5 ml. of hot water, add a slight excess of sodium hydroxide to liberate chlorothen base, and filter: the clear filtrate responds to the tests for *Citrate,* page 808.

Melting range, page 814—Chlorothen Citrate melts between 112° and 116°. On further heating it gradually solidifies and remelts between 125° and 140° with decomposition.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Chlorothen Citrate, previously dried in vacuum over phosphorus pentoxide for 5 hours, exhibits maxima only at the same wavelengths as that of NF Chlorothen Citrate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Chlorothen Citrate in 0.5 *N* sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Chlorothen Citrate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 243 mμ do not differ by more than 2.5 percent.

Loss on drying, page 814—Dry Chlorothen Citrate in vacuum over phosphorus pentoxide for 5 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Chlorothen Citrate yields not more than 0.1 percent of residue on ignition.

Assay—Transfer to a beaker about 600 mg. of Chlorothen Citrate, previously dried in vacuum over phosphorus pentoxide for 5 hours and accurately weighed, and dissolve it in 80 ml. of glacial acetic acid. Titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically, using suitable electrodes. Each ml. of 0.1 *N* perchloric acid is equivalent to 24.40 mg. of $C_{14}H_{18}ClN_3S \cdot C_6H_8O_7$.

Packaging and storage—Preserve Chlorothen Citrate in tight, light-resistant containers.

CATEGORY—Antihistaminic.

USUAL DOSE—**25 mg.** every 3 or 4 hours, should not exceed 150 mg. in a 24-hour period.

Chlorothen Citrate Tablets

Chlorothen Citrate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{14}H_{18}ClN_3S \cdot C_6H_8O_7$.

Identification—To a portion of finely powdered Chlorothen Citrate Tablets, equivalent to about 50 mg. of chlorothen citrate, add 5 ml. of water and 3 ml. of ammonia T.S., and extract the liberated base with two 10-ml. portions of ether. Wash the combined ether extracts with 2 ml. of water, and evaporate the ether extracts to dryness. The residue so obtained responds to *Identification test A* under *Chlorothen Citrate,* page 158.

Ultraviolet absorption, page 866—The solution employed for the measurement of ultraviolet absorbance in the *Assay* exhibits an absorbance maximum at 313 ± 1 mμ.

Disintegration, page 878—The disintegration time limit for Chlorothen Citrate Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Chlorothen Citrate Tablets meet the requirements of the content uniformity test for tablets.

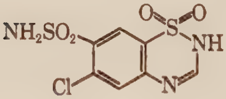
Assay—Weigh and finely powder not less than 20 Chlorothen Citrate Tablets. Weigh accurately a portion of the powder, equivalent to about 40 mg. of chlorothen citrate, and transfer to a 100-ml. volumetric flask. Add 25 ml. of formic acid, shake mechanically for 1 hour, and dilute to volume with water. Centrifuge the mixture and transfer 25.0 ml. of the clear supernatant liquid to a 250-ml. separator. Add 20 ml. of ether, shake carefully, and draw the aqueous phase into a second 250-ml. separator. Wash the ether phase with two 10-ml. portions of water, adding the washings to the second separator, and discard the ether. To the acid solution slowly add sodium hydroxide solution (1 in 4), in portions, until the solution is distinctly alkaline, cool the solution to room temperature, add 50 ml. of ether, shake carefully, and transfer the aqueous phase to a third 250-ml. separator containing 50 ml. of ether. Shake the third separator carefully, and discard the aqueous phase. Wash the ether extracts in the two separators, in succession, with one 20-ml. portion of water, and discard the water. Extract the separate ether phases successively with three 20-ml. portions of 0.5 *N* sulfuric acid, combine the acid extracts in a 100-ml. volumetric flask, dilute with the acid to volume, and mix. Transfer 20.0 ml. of the solution to another 100-ml. volumetric flask, make to volume with 0.5 *N* sulfuric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Chlorothen Citrate Reference Standard, in the same medium, at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 313 mμ with a suitable spectrophotometer, using 0.5 *N* sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{14}H_{18}ClN_3S.C_6H_8O_7$ in the portion of the Tablets taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Chlorothen Citrate Tablets in tight containers.

Tablets available—Chlorothen Citrate Tablets usually available contain the following amount of chlorothen citrate: 25 mg.

CATEGORY and DOSE—See Chlorothen Citrate.

Chlorothiazide*



6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide

$C_7H_6ClN_3O_4S_2$ Mol. wt. 295.72

Chlorothiazide contains not less than 98.0 percent and not more than 100.5 percent of $C_7H_6ClN_3O_4S_2$, calculated on the dried basis.

Description—Chlorothiazide occurs as a white or practically white, odorless, crystalline powder. It melts at about 355°.

Solubility—Chlorothiazide is very slightly soluble in water. It is freely soluble in dimethylformamide and in dimethyl sulfoxide, and is slightly soluble in methanol and in pyridine. It is practically insoluble in ether, in benzene, and in chloroform.

Identification—Fuse about 100 mg. of Chlorothiazide with a pellet of sodium hydroxide: the ammonia fumes produced turn moistened red litmus paper blue. The fusion mixture responds to the test for *Sulfite*, page 810.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Chlorothiazide, previously dried at 105° for 1 hour, exhibits maxima only at the same wavelengths as that of NF Chlorothiazide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Chlorothiazide in 0.1 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Chlorothiazide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 292 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Chlorothiazide at 105° for 1 hour: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Chlorothiazide yields not more than 0.1 percent of residue on ignition.

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* Patented. See notice, page ii.

Chloride—Dissolve about 1 g. of Chlorothiazide, accurately weighed, in a mixture of 10 ml. of water and 10 ml. of sodium hydroxide solution (1 in 10). Cool in an ice bath, and add 20 ml. of water and 5 ml. of nitric acid. A flocculent, white precipitate is formed. Titrate potentiometrically, using a silver-silver chloride electrode system and 0.05 *N* silver nitrate as the titrant. Each ml. of 0.05 *N* silver nitrate is equivalent to 1.778 mg. of Cl. Not more than 0.05 percent of Cl is found.

Selenium—A *Test Preparation* prepared with 200 mg. of Chlorothiazide meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Heavy metals, *Method II*, page 806—The heavy metals limit for Chlorothiazide is 10 parts per million.

Diazotizable substances—

Standard preparation—Transfer 20.0 mg. of NF 4-Amino-6-chloro-1,3-benzenedisulfonamide Reference Standard to a 100-ml. volumetric flask, dissolve in acetone, dilute to volume with acetone, and mix. Transfer 4.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with acetone, and mix. Each ml. of the *Standard preparation* contains 8 mcg. of the reagent.

Test preparation—Transfer 80.0 mg. of Chlorothiazide to a 100-ml. volumetric flask, dilute to volume with acetone, and mix.

Procedure—Transfer 1.0 ml. each of the *Standard preparation*, of the *Test preparation*, and of acetone to serve as the blank to separate tubes. To each tube add 9.0 ml. of 1 *N* hydrochloric acid and 0.1 ml. of freshly prepared sodium nitrite solution (1 in 25), mix, and allow to stand for 1 minute. Add 0.8 ml. of ammonium sulfamate solution (1 in 50), mix, allow to stand for 3 minutes, add 0.8 ml. of *N*-1-naphthylethylenediamine dihydrochloride solution in 50 percent alcohol (1 in 50), and mix. After 2 minutes, concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 518 mμ, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance of the solution from the *Test preparation* does not exceed that of the solution from the *Standard preparation*, corresponding to not more than 1 percent of diazotizable substances.

Assay—Dissolve about 500 mg. of Chlorothiazide, accurately weighed, in 80 ml. of dimethylformamide, observing precautions against absorption of atmospheric carbon dioxide. Add 3 drops of a 1 in 100 solution of bromothymol blue in dimethylformamide, and titrate with 0.1 *N* sodium methoxide to a full turquoise-blue endpoint. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium methoxide is equivalent to 29.57 mg. of $C_7H_6ClN_3O_4S_2$.

Packaging and storage—Preserve Chlorothiazide in well-closed containers.

CATEGORY—Diuretic; antihypertensive.

USUAL DOSE—Diuretic, **500 mg.** one or two times a day. Antihypertensive, **250 mg.** three times a day.

USUAL DOSE RANGE—Diuretic, **500 mg.** to **1 g.** Antihypertensive, **250** to **500 mg.**

Chlorothiazide Oral Suspension

Chlorothiazide Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_7H_6ClN_3O_4S_2$.

Identification—The ultraviolet absorption spectrum of the solution of chlorothiazide prepared from Chlorothiazide Oral Suspension as directed in the *Assay* exhibits maxima and minima at the same wavelengths as that of a solution of NF Chlorothiazide Reference Standard, prepared as directed in the *Assay*, similarly measured.

pH, page 824—The pH of Chlorothiazide Oral Suspension is between 3.5 and 4.0.

Assay—Transfer to a 250-ml. volumetric flask an accurately measured volume of Chlorothiazide Oral Suspension, equivalent to about 250 mg. of chlorothiazide, dilute to volume with 0.1 *N* sodium hydroxide, and mix. Transfer 10.0 ml. of this solution to a 100-ml volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Transfer 50.0 ml. of this last solution to a 125-ml. separator, and wash with two 25-ml. portions of chloroform, discarding the washings. Transfer 10.0 ml. of the washed solution to a 100-ml. volumetric flask, dilute to volume with 0.1 *N* sodium hydroxide, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Chlorothiazide Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 292 mμ, with a suitable spectrophotometer, using 0.1 N sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_7H_6ClN_3O_4S_2$ in each ml. of the Suspension taken by the formula $25 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Suspension taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Chlorothiazide Oral Suspension in tight containers.

Suspension available—Chlorothiazide Oral Suspension usually available contains the following amount of chlorothiazide: 250 mg. in 5 ml.

Category and Dose—See Chlorothiazide.

Chlorothiazide Tablets

Chlorothiazide Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_7H_6ClN_3O_4S_2$.

Identification—

A: The polarogram (see page 847) of the solution employed for measurement in the *Assay* of Chlorothiazide Tablets exhibits a half-wave potential ($E_{1/2}$) within 1 percent of that of NF Chlorothiazide Reference Standard, similarly measured.

B: Powder 1 Chlorothiazide Tablet, and fuse it with a pellet of sodium hydroxide: the fusion mixture responds to the *Identification test* under *Chlorothiazide*, page 160.

Disintegration, page 878—The disintegration time limit for Chlorothiazide Tablets is 30 minutes.

Weight variation, page 901—Chlorothiazide Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Chlorothiazide Tablets. Weigh accurately a portion of the powder, equivalent to about 250 mg. of chlorothiazide, and transfer to a 100-ml. volumetric flask. Add 20 ml. of dimethylformamide, shake for 5 minutes, then dilute to volume with water. Pipet 10.0 ml. of the solution into a 100-ml. volumetric flask, and add 50 ml. of 1 M ammonium chloride and 3 ml. of a 1 in 500 solution of alkyl phenoxy polyethoxy ethanol. Dilute to volume with water, and mix. Transfer a portion of this solution to a polarographic cell. De-aerate by bubbling nitrogen through the sample solution for 10 minutes. Insert the dropping mercury electrode of a suitable polarograph, and with a drop-time of 3 to 4 seconds, record the polarogram from -1.00 volt to -1.75 volts, using a saturated calomel electrode as the reference electrode. Determine the height of the diffusion current $[(i_d)_U]$ as the difference between the residual current and the diffusion current plateau. Concomitantly and similarly determine the diffusion current $[(i_d)_S]$ of a solution containing about 250 mcg. of NF Chlorothiazide Reference Standard in each ml. and prepared as directed for the sample solution. Calculate the quantity, in mg., of $C_7H_6ClN_3O_4S_2$ in the portion of the Tablets taken by the formula $C \times [(i_d)_U/(i_d)_S]$, in which C is the exact concentration, in mcg. per ml., of NF Chlorothiazide Reference Standard in the Reference Standard solution.

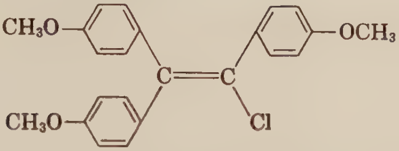
Packaging and storage—Preserve Chlorothiazide Tablets in well-closed containers.

Tablets available—Chlorothiazide Tablets usually available contain the following amounts of chlorothiazide: 250 and 500 mg.

Category and Dose—See Chlorothiazide.

Chlorothiazide, Sodium, for Injection, page 641

Chlorotrianisene



Chlorotris(*p*-methoxyphenyl)ethylene

$C_{23}H_{21}ClO_3$ Mol. wt. 380.88

Chlorotrianisene, dried at 80° for 18 hours, contains not less than 97.0 percent and not more than 103.0 percent of $C_{23}H_{21}ClO_3$.

Description—Chlorotrianisene occurs as small white crystals, or as a crystalline powder. It is odorless, and is stable in air.

Solubility—Chlorotrianisene is very slightly soluble in water. It is slightly soluble in alcohol and in methanol, and is freely soluble in acetone, in benzene, and in chloroform. It is practically insoluble in 2,2,4-trimethylpentane.

Melting range, page 814—Chlorotrianisene melts between 115° and 117°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Chlorotrianisene, previously dried at 80° for 18 hours, exhibits maxima only at the same wavelengths as that of NF Chlorotrianisene Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Chlorotrianisene in chloroform exhibits maxima and minima at the same wavelengths as that of NF Chlorotrianisene Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 310 $m\mu$ do not differ by more than 3 percent.

pH, page 824—The pH of a saturated solution of Chlorotrianisene is between 5.0 and 7.0.

Loss on drying, page 814—Dry Chlorotrianisene at 80° for 18 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Chlorotrianisene yields not more than 1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Chlorotrianisene is 20 parts per million.

Assay—Transfer to a 100-ml. flask 500 mg. of Chlorotrianisene, previously dried at 80° for 18 hours and accurately weighed, add 15 ml. of dehydrated alcohol, connect the flask to a reflux condenser, and begin heating gently. When the Chlorotrianisene has dissolved and the alcohol is boiling, cautiously add through the condenser about 2 g. of clean sodium, cut in small pieces. Reflux for not less than 1 hour, shaking frequently (there must be a visible excess of sodium present at the end of 1 hour, add more sodium if necessary); then, while the solution is still boiling, cautiously add alcohol to decompose the excess sodium. Continue heating for 15 minutes after the last trace of sodium has disappeared. Rinse the condenser with small portions of water, and transfer the reaction mixture to a 400-ml. beaker, rinsing the flask with about 125 ml. of water. Cool the solution and add 15 ml. of nitric acid and 25.0 ml. of 0.1 *N* silver nitrate, and mix. When the precipitate has coagulated, filter, and wash the filter with water. Add 10 ml. of ferric ammonium sulfate T.S. to the filtrate, and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 38.09 mg. of $C_{23}H_{21}ClO_3$.

Packaging and storage—Preserve Chlorotrianisene in tight containers.

Category—Estrogen.
Usual dose—**24 mg.** daily.
Usual dose range—**12 to 50 mg.**

Chlorotrianisene Capsules

Chlorotrianisene Capsules contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{23}H_{21}ClO_3$.

Identification—The assay sample solution prepared from Chlorotrianisene Capsules and the solution prepared from NF Chlorotrianisene Reference Standard in the *Assay* exhibit similar ultraviolet absorption spectra.

Content uniformity, *Method I*, page 798—Chlorotrianisene Capsules meet the requirements of the content uniformity test for capsules.

Assay—

Chromatographic column—Pack a pledget of glass wool in the base of a chromatographic tube (25 × 300-mm. test tube to which is fused a 5-cm. length of 6 or 8-mm. tubing) with the aid of a tamping rod of stainless steel, aluminum, or glass, at least 31 cm. long and having a terminal disk with a diameter about 1 mm. less than that of the chromatographic tube. To 7.0 g. of purified siliceous earth in a 150-ml. beaker, add 8.0 ml. of nitromethane, and incorporate by kneading thoroughly with a flexible spatula blade until the mixture is fluffy. Transfer to the chromatographic tube in three approximately equal portions, tamping gently to compress the material to a uniform mass.

Assay preparation for hard gelatin capsules—Remove as completely as possible, the contents of not less than 20 Chlorotrianisene Capsules and weigh accurately. Mix the combined contents thoroughly, and transfer an accurately weighed quantity of the powder, equivalent to about 12 mg. of chlorotrianisene, to a 100-ml. volumetric flask. Add 75 ml. of *n*-heptane, shake for 30 minutes, dilute to volume with *n*-heptane, and mix.

Assay preparation for soft capsules—Weigh accurately not less than 10 Chlorotrianisene Capsules in a tared weighing vessel. Transfer the weighed Capsules to another dish. Carefully open the Capsules, without loss of the shell material, and transfer the contents to a 50-ml. beaker. Wash the emptied capsules with several portions of ether, and allow them to dry in a jet of air until the odor of ether is no longer perceptible. Weigh the empty capsules in the original tared weighing vessel: the difference represents the weight of the contents of the capsules. Transfer an accurately weighed portion of the contents of the capsules, equivalent to about 12 mg. of chlorotrianisene, to a 100-ml. volumetric flask, add *n*-heptane to volume, and mix.

Procedure—Transfer 10.0 ml. of the *Assay preparation* to the prepared column. Wash the column with 40 ml. of *n*-heptane, and discard the washings. Elute with 175 ml. of *n*-heptane, collecting the eluate in a 250-ml. conical flask. Evaporate the eluate to dryness, dissolve the residue in chloroform, and transfer to a 100-ml. volumetric flask. Wash the receiver with chloroform, transfer the washings to the volumetric flask, add chloroform to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Chlorotrianisene Reference Standard, in the same medium, at a concentration of about 12 mcg. per ml., in 1-cm. cells, at the maximum absorbance at about 310 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{23}H_{21}ClO_3$ in the portion of the Capsules taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Chlorotrianisene Capsules in well-closed containers protected from excessive heat, cold, and moisture.

Labeling—The container label indicates the vehicle used in the Chlorotrianisene Capsules.

Capsules available—Chlorotrianisene Capsules usually available contain the following amounts of chlorotrianisene: 12, 25, and 72 mg.

CATEGORY and DOSE—See Chlorotrianisene.

Chlorpheniramine Maleate Injection

Chlorpheniramine Maleate Injection is a sterile solution of chlorpheniramine maleate in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{19}ClN_2.C_4H_4O_4$.

Identification—

A: Dilute a volume of Chlorpheniramine Maleate Injection, equivalent to about 50 mg. of chlorpheniramine maleate, with 0.01 *N* hydrochloric acid to 25 ml., and proceed as directed under *Identification—Organic Nitrogenous Bases*, page 810, beginning with "Transfer the liquid to a separator. . . .": the Injection meets the requirements of the test.

B: Evaporate a volume of Chlorpheniramine Maleate Injection, equivalent to about 25 mg. of chlorpheniramine maleate, on a steam bath to dryness, and dry the residue at 105° for 1 hour: it melts between 128° and 135°, page 814.

pH, page 824—The pH of Chlorpheniramine Maleate Injection is between 4.0 and 5.2.

Other requirements—Chlorpheniramine Maleate Injection meets the requirements under *Injections*, page 810.

Assay—Proceed with Chlorpheniramine Maleate Injection as directed under *Salts of Organic Nitrogenous Bases*, page 865, but for the determination of A_S, dissolve about 25 mg. of USP Chlorpheniramine Maleate Reference Standard, accurately weighed, in 20 ml. of 0.1 N sulfuric acid, and treat this solution the same as the portion of Injection being assayed. Concomitantly determine the absorbances of the solutions at the maximum occurring at about 264 mμ, with a suitable spectrophotometer. Calculate the quantity, in mg., of $C_{16}H_{19}ClN_2 . C_4H_4O_4$ in each ml. of the Injection taken by the formula $0.05 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Chlorpheniramine Maleate Reference Standard in the *Standard Preparation*, and V is the volume, in ml., of Injection taken.

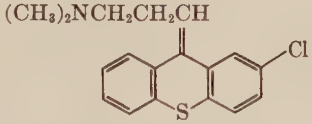
Packaging and storage—Preserve Chlorpheniramine Maleate Injection in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

Injections available—Chlorpheniramine Maleate Injection usually available contains the following amounts of chlorpheniramine maleate: 10 mg. in 1 ml.; 100 mg. in 10 ml.; and 200 mg. in 2 ml.

CATEGORY—Antihistaminic.

USUAL DOSE OF CHLORPHENIRAMINE MALEATE—Parenteral, **10** to **20 mg.**

Chlorprothixene*



(E)-2-Chloro-N,N-dimethylthioxanthene-$\Delta^{9,\gamma}$-propylamine

$C_{18}H_{18}ClNS$ Mol. wt. 315.87

Chlorprothixene contains not less than 99.0 percent and not more than 101.0 percent of $C_{18}H_{18}ClNS$, calculated on the dried basis.

Description—Chlorprothixene occurs as a yellow, crystalline powder, having a slight amine-like odor.

Solubility—Chlorprothixene is practically insoluble in water. It is soluble in alcohol and in ether, and is freely soluble in chloroform.

Identification—

A: Dissolve about 10 mg. of Chlorprothixene in 2 ml. of sulfuric acid: the resulting orange solution exhibits a strong yellow fluorescence under ultraviolet light.

B: Dissolve about 10 mg. of Chlorprothixene in 2 ml. of nitric acid: a light red solution forms. Dilute the solution with 5 ml. of water: the solution exhibits a green fluorescence under ultraviolet light.

Melting range, page 814—Chlorprothixene melts between 96.5° and 101.5°.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 10 solution of Chlorprothixene, previously dried in vacuum over phosphorus pentoxide at 60° for 4 hours, in carbon disulfide, exhibits maxima only at the same wavelengths as that of NF Chlorprothixene Reference Standard, similarly measured.

Ultraviolet Absorption, page 866—A 1 in 20,000 solution of Chlorprothixene in 0.1 N hydrochloric acid exhibits an absorbance maximum at 324 ± 2 mμ, and its absorptivity at that maximum is within 2 percent of the absorptivity of a solution of NF Chlorprothixene Reference Standard similarly measured. A 1 in 100,000 solution of Chlorprothixene in 0.1 N hydrochloric acid exhibits an absorbance maximum at 267 ± 2 mμ, and its absorptivity at that maximum is within ± 2 percent of the absorptivity of a solution of NF Chlorprothixene Reference Standard similarly measured.

Loss on drying, page 814—Dry Chlorprothixene in vacuum over phosphorus pentoxide at 60° for 4 hours: it loses not more than 0.1 percent of its weight.

Residue on ignition, page 858—Chlorprothixene yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Chlorprothixene is 20 parts per million.

Assay—Dissolve about 800 mg. of chlorprothixene, accurately weighed, in 80 ml. of chloroform, add 3 drops of methanolic methyl red T.S., and titrate with 0.1 N perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 31.59 mg. of $C_{18}H_{18}ClNS$.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Chlorprothixene in tight, light-resistant containers.

Category—Tranquilizer (major).

Usual dose range—Moderate anxiety, **10 mg.** three or four times a day (up to 60 mg. daily); severe neurotic and psychotic states, **25** to **50 mg.** three or four times daily (up to 600 mg. daily).

Chlorprothixene Tablets

Chlorprothixene Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{18}ClNS$.

Identification—

A: A portion of finely powdered Chlorprothixene Tablets, equivalent to about 10 mg. of chlorprothixene, responds to *Identification test B* under *Chlorprothixene*, page 165.

B: The ultraviolet absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of a 1 in 20,000 solution of NF Chlorprothixene Reference Standard in 0.5 *N* hydrochloric acid, similarly measured.

Disintegration, page 878—The disintegration time limit for Chlorprothixene Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—[Note: Use low-actinic glassware.] Chlorprothixene Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Crush one tablet in a suitable container, add 5 ml. of dimethylformamide, and let stand for about 20 to 30 minutes. Dilute this solution quantitatively and stepwise, if necessary, with 0.1 *N* sulfuric acid, filtering prior to final dilution, to provide a solution containing approximately 50 mcg. of chlorprothixene per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Chlorprothixene Reference Standard, in the same medium at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 324 mμ, with a suitable spectrophotometer, using 0.1 *N* sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{18}H_{18}ClNS$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of chlorprothixene, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of chlorprothixene in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

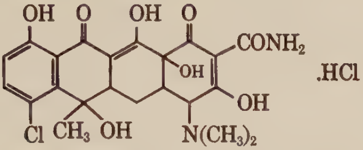
Assay—[Note: Use low-actinic glassware.] Weigh and finely powder not less than 20 Chlorprothixene Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of chlorprothixene, to a glass-stoppered 125-ml. conical flask, add 50 ml. of ether, and shake the mixture mechanically for 45 minutes. Filter the suspension through glass wool into a separator, and wash the flask and filter with three 10-ml. portions of ether. Extract the combined filtrate and washings with four 30-ml. portions of 0.5 *N* hydrochloric acid, combining the extracts in a 200-ml. volumetric flask. Dilute the extracts to volume with 0.5 *N* hydrochloric acid, and mix. Transfer 10.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Chlorprothixene Reference Standard, in the same medium, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 324 mμ, with a suitable spectrophotometer, using water containing 10 ml. of 0.5 *N* hydrochloric acid per 50 ml. as the blank. Calculate the quantity, in mg., of $C_{18}H_{18}ClNS$ in the portion of the Tablets taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Chlorprothixene Tablets in well-closed, light-resistant containers.

Tablets available—Chlorprothixene Tablets usually available contain the following amounts of chlorprothixene: 10, 25, 50 and 100 mg.

Category and Dose—See Chlorprothixene.

Chlortetracycline Hydrochloride



7-Chlorotetracycline Hydrochloride

7-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide Monohydrochloride

$C_{22}H_{23}ClN_2O_8 . HCl$ Mol. wt. 515.35

Chlortetracycline Hydrochloride contains not less than 90.0 percent of $C_{22}H_{23}ClN_2O_8 . HCl$. Chlortetracycline Hydrochloride conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Chlortetracycline Hydrochloride occurs as a yellow, crystalline powder. It is odorless and has a bitter taste. It is stable in air but is slowly affected by light. Its 1 in 200 solution has a pH of about 3.

Solubility—Chlortetracycline Hydrochloride is sparingly soluble in water, and is slightly soluble in alcohol. It is soluble in solutions of alkali hydroxides and carbonates. It is practically insoluble in acetone, in chloroform, in dioxane, and in ether.

Packaging and storage—Preserve Chlortetracycline Hydrochloride in tight containers, protected from light.

CATEGORY—Antibacterial; antiprotozoan.

USUAL DOSE—**250 mg.** four times a day.

USUAL DOSE RANGE—**250 to 500 mg.**

Chlortetracycline Hydrochloride Capsules

Chlortetracycline Hydrochloride Capsules contain not less than 85.0 percent of the labeled amount of $C_{22}H_{23}ClN_2O_8 . HCl$. Chlortetracycline Hydrochloride Capsules conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Chlortetracycline Hydrochloride Capsules in tight, light-resistant containers.

Capsules available—Chlortetracycline Hydrochloride Capsules usually available contain the following amounts of chlortetracycline hydrochloride: 50, 100, and 250 mg.

CATEGORY and DOSE—See Chlortetracycline Hydrochloride.

Chlortetracycline Hydrochloride for Injection

Chlortetracycline Hydrochloride for Injection is a sterile, dry mixture of chlortetracycline hydrochloride with a suitable buffer, the latter usually consisting of an amino acid. It contains not less than 85.0 percent of the labeled amount of $C_{22}H_{23}ClN_2O_8 . HCl$. Chlortetracycline Hydrochloride for Injection conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Chlortetracycline Hydrochloride for Injection in single-dose or multiple-dose containers.

Labeling—Chlortetracycline Hydrochloride for Injection complies with the requirements for *Labeling* under *Injections*, page 810. The container label indicates the solvent recommended for preparing a solution for injection.

Size available—Chlortetracycline Hydrochloride for Injection usually available contains the following amount of chlortetracycline hydrochloride: 500 mg.

CATEGORY and DOSE—See Chlortetracycline Hydrochloride.

Ophthalmic Chlortetracycline Hydrochloride

Ophthalmic Chlortetracycline Hydrochloride is a sterile, dry mixture of chlortetracycline hydrochloride with a suitable buffer. It contains not less than 85.0 percent of the labeled amount of $C_{22}H_{23}ClN_2O_8.HCl$. It may contain suitable bacteriostatic agents and diluents. Ophthalmic Chlortetracycline Hydrochloride conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Ophthalmic Chlortetracycline Hydrochloride in tight containers.

Size available—Ophthalmic Chlortetracycline Hydrochloride usually available contains the following amount of chlortetracycline hydrochloride: 25 mg. in each vial.

Category—Antibacterial.

Application—Topically 1 or 2 drops of a 0.5 percent solution every 2 hours.

Chymotrypsin

Chymotrypsin is a proteolytic enzyme crystallized from an extract of the pancreas gland of the ox, *Bos taurus* Linné (Fam. *Bovidæ*). When assayed as directed herein, it contains not less than 1000 NF Chymotrypsin Units in each mg., calculated on the dried basis, and not less than 90.0 percent and not more than 110.0 percent of the labeled potency.

Note: Determine the suitability of the substrate and check the adjustment of the spectrophotometer by performing the assay using NF Chymotrypsin Reference Standard. Determine the suitability of the substrate in the limit test for Trypsin by using the appropriate amount of NF Trypsin Crystallized Reference Standard.

Description—Chymotrypsin occurs as a white to yellowish white, odorless, crystalline or amorphous powder.

Solubility test—An amount of Chymotrypsin, equivalent to 100,000 NF Chymotrypsin Units, is soluble in 10 ml. of water or in 10 ml. of saline T.S.

Loss on drying, page 814—Dry Chymotrypsin in a vacuum oven at 60° for 4 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Chymotrypsin yields not more than 2.5 percent of residue on ignition.

Trypsin—

Chymotrypsin solution—Dissolve 100 mg. of Chymotrypsin in 10.0 ml. of water.

Tris(hydroxymethyl)aminomethane buffer 0.08 M, pH 8.1—Dissolve 294 mg. of calcium chloride in 40 ml. of 0.2 *M* tris(hydroxymethyl)aminomethane, adjust the pH to 8.1 with 1 *N* hydrochloric acid, and dilute to 100 ml. with water.

Substrate solution—Transfer 98.5 mg. of *p*-toluenesulfonyl-L-arginine methyl ester hydrochloride, suitable for assaying trypsin, into a 25-ml. volumetric flask. Add 5 ml. of *0.08 M Tris(hydroxymethyl)aminomethane buffer, pH 8.1,* and swirl until the substrate dissolves. Add 0.25 ml. of methyl red—methylene blue T.S., and dilute to volume with water.

Procedure—By means of a micropipet transfer 50 μl. of the *Chymotrypsin solution* to a depression on a white spot plate. Add 0.2 ml. of the *Substrate solution,* start a stop watch and allow it to run for exactly 3 minutes: no purple color develops within 3 minutes, indicating the presence of no more than 1 percent of trypsin.

Salmonella, page 862—The test for *Salmonella* in Chymotrypsin is negative.

Assay—

Fifteenth molar phosphate buffer, pH 7.0—Dissolve 4.54 g. of monobasic potassium phosphate in sufficient water to make 500 ml. of solution. Dissolve 4.73 g. of anhydrous dibasic sodium phosphate in sufficient water to make 500 ml. of solution. Mix 38.9 ml. of the monobasic potassium phosphate solution with 61.1 ml. of dibasic sodium phosphate solution. If necessary, adjust the pH to 7.0 by the dropwise addition of dibasic sodium phosphate solution.

Substrate solution—Dissolve 23.7 mg. of *N*-acetyl-L-tyrosine ethyl ester, suitable for use in assaying Chymotrypsin, in about 50 ml. of *Fifteenth molar phosphate* *buffer, pH 7.0*, with warming. When cool, dilute to 100 ml. with additional pH 7.0 buffer. (*Substrate solution* may be stored in the frozen state and used after thawing; it is important, however, to freeze immediately after preparation.)

Chymotrypsin solution—Accurately weigh and dissolve a sufficient amount of the sample being assayed in 0.001 *N* hydrochloric acid to produce a solution containing between 12 and 16 NF Chymotrypsin Units per ml. The dilution will be correct if, during the conduct of the assay, there is a change in absorbance of between 0.008 and 0.012 in each 30-second interval.

Procedure—Conduct the assay in a suitable spectrophotometer equipped to maintain a temperature of 25° ± 0.1° in the cell compartment. The temperature in the reaction cell should be determined before and after the measurement of absorbance to assure that the temperature does not change by more than 0.5°. Pipet 0.2 ml. of 0.001 *N* hydrochloric acid and 3.0 ml. of the *Substrate solution* into a 1-cm. cell. Place this cell in the spectrophotometer and adjust the instrument so that the absorbance will read 0.200 at 237 mμ. Pipet 0.2 ml. of *Chymotrypsin solution* containing between 12 and 16 NF Chymotrypsin Units per ml. into another 1-cm. cell, add 3 ml. of the *Substrate solution*, and place the cell in the spectrophotometer. (*This order of addition must be followed.*) At the time the *Substrate solution* is added, start a stop watch and read the absorbance at 30-second intervals for at least 5 minutes. Repeat the procedure on the same dilution at least once. Absolute absorbance values are of less importance than the constancy of the rate of change of absorbance. If the rate of change does not remain constant for at least 3 minutes, repeat the run and, if necessary, use a lower concentration. The duplicate run at the same dilution should match the first run in rate of absorbance change. Determine the average absorbance change per minute, using only the values within the 3-minute portion of the curve where the rate of absorbance change is constant. Plot a curve of absorbance against time. One NF Chymotrypsin Unit is the activity causing a change in absorbance of 0.0075 per minute under the conditions specified in this assay. Calculate the number of NF Chymotrypsin Units per mg. by the formula $(A_2 - A_1)/(T \times W \times 0.0075)$ in which A_1 is the absorbance straight line final reading, A_2 is the absorbance straight line initial reading, T is the elapsed time in minutes between the initial and final readings, and W is the weight, in mg., of Chymotrypsin in the volume of solution used in determining the absorbance.

Packaging and storage—Preserve Chymotrypsin in tight containers and avoid excessive heat.

CATEGORY—Proteolytic.

USUAL DOSE RANGE—Intramuscular, 2500 to 5000 NF Units one to three times a day.

Sterile Chymotrypsin

Sterile Chymotrypsin contains not less than 80.0 percent and not more than 120.0 percent of the labeled potency of chymotrypsin.

Description and other requirements—Sterile Chymotrypsin conforms to the *Description* and meets the other requirements under *Chymotrypsin*, page 168.

Identification—Prepare a *Substrate solution* as directed in the *Identification test* under *Chymotrypsin Injection*, page 170. Reconstitute the contents of one vial of Sterile Chymotrypsin in 1 ml. of saline T.S., transfer 0.2 ml. to a spot plate, and add 0.2 ml. of the *Substrate solution:* a purple color is produced within three minutes (*distinction from trypsin which produces no purple color within three minutes*).

Completeness of solution—Sterile Chymotrypsin dissolves completely in the solvent and in the concentration recommended in the labeling.

Sterility—Sterile Chymotrypsin meets the requirements under *Sterility Tests*, page 874.

Assay—Proceed as directed in the *Assay* under *Chymotrypsin*, page 168, but use the following as the *Chymotrypsin solution:* Dissolve the contents of one vial of Sterile Chymotrypsin in 5.0 ml. of 0.001 *N* hydrochloric acid. Dilute an accurately measured volume (V, in ml.) of this solution, equivalent to about 300 NF Chymotrypsin Units, to 25.0 ml. with 0.001 *N* hydrochloric acid. Calculate the number of NF Chymotrypsin Units per vial by the formula $300 \times (5/V)(A_2 - A_1)/(T \times 2.4 \times 0.0075)$, in which A_1 is the absorbance straight-line final reading, A_2 is the absorbance straight-line initial reading, T is the elapsed time in minutes between the initial and final reading, and 2.4 is the number of NF Chymotrypsin Units present in the sample on which the absorbance was determined.

Packaging and storage—Preserve Sterile Chymotrypsin in single-dose containers, preferably of Type I glass.

Labeling—Sterile Chymotrypsin complies with the requirements for *Labeling* under *Injections,* page 810.

Sizes available—Sterile Chymotrypsin usually available contains the following amount of chymotrypsin: 750 NF Chymotrypsin Units.

CATEGORY—See Chymotrypsin.

APPLICATION—For zonule lysis, 150 to 500 NF Units as a 1:5000 solution.

Chymotrypsin Injection

Chymotrypsin Injection is a sterile solution of Chymotrypsin in water for injection or in aqueous gelatin solution. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled potency.

Identification—Prepare a *Substrate solution* as follows: Transfer 237.0 mg. of *N*-acetyl-L-tyrosine ethyl ester, suitable for use in assaying chymotrypsin, to a 100-ml. volumetric flask, add 2 ml. of alcohol, swirl until solution is effected. Add 20 ml. of *Fifteenth molar phosphate buffer, pH 7.0,* prepared as directed in the *Assay* under *Chymotrypsin,* page 168, add 1 ml. of methyl red-methylene blue T.S., and dilute to volume with water. Mix 0.2 ml. of this solution with 0.05 ml. of Chymotrypsin Injection on a spot plate: a purple color is produced *(distinction from trypsin which produces no purple color within three minutes).*

Other requirements—Chymotrypsin Injection meets the requirements under *Injections,* page 810.

pH, page 824—The pH of Chymotrypsin Injection is between 3.9 and 4.1.

Assay—Dilute an accurately measured volume of Chymotrypsin Injection with 0.001 *N* hydrochloric acid to produce a solution containing between 12 and 16 NF Chymotrypsin Units per ml. Proceed as directed in the *Assay* under *Chymotrypsin,* page 168. Calculate the number of NF Units of Chymotrypsin in each ml. of the Injection taken by the formula $(A_2 - A_1)/(T \times V \times 0.0075)$, in which A_1 is the absorbance straight line final reading, A_2 is the absorbance straight line initial reading, T is the elapsed time in minutes between the initial and final readings, and V is the volume of Injection, taking into account the dilutions employed, present in the 0.2-ml. aliquot used in determining the absorbance.

Packaging and storage—Preserve Chymotrypsin Injection in single-dose or in multiple-dose containers, preferably of Type I glass, in a refrigerator. Avoid freezing.

Injections available—Chymotrypsin Injection usually available contains the following amounts of chymotrypsin: 5000 NF Chymotrypsin Units in 1 ml. and 25,000 Units in 5 ml.

CATEGORY and DOSE—See Chymotrypsin.

Cinnamon

Cinnamon is the dried bark of *Cinnamomum loureirii* Nees (Fam. *Lauraceæ*). Cinnamon contains, in each 100 g., not less than 2.5 ml. of volatile oil.

Unground Cinnamon occurs in quills up to 30 cm. long and 4 cm. in diameter, the bark from 0.5 to 7.0 mm. in thickness, or in broken irregular pieces or in flattened slabs up to 10 mm. in thickness. The outer surface of the bark is light brown to dark purplish brown, often with grayish patches of crustose lichens and numerous bud scars, finely longitudinally wrinkled when from young twigs, otherwise more or less rough from corky patches surrounding the lenticels. The inner surface is reddish brown to dark brown, granular, and slightly striate. The fracture is short. The odor is characteristically aromatic. The taste is sweetish, aromatic, and pungent.

Histology—Sections of Cinnamon show a narrow outer layer of more or less lignified cork cells followed by a cortex of starch-bearing parenchyma with scattered stone cells, mucilage and oil cells, a pericycle containing a nearly continuous zone of stone cells among which are small groups of pericyclic fibers with thickened and slightly lignified walls, and a broad phloem traversed by phloem rays 1 to 3 cells wide, the cells containing either starch or very small acicular crystals of calcium oxalate. The phloem strands consist largely of parenchyma cells among which occur scattered inconspicuous islets of sieve, phloem fibers which are isolated or in groups of 2 to 20, and numerous mucilage and oil cells. The parenchyma cells usually are filled with starch or contain very small acicular crystals of calcium oxalate, the latter mostly localized in the phloem ray cells. The lumina of parenchyma cells, stone cells, and fibers are frequently filled with an amorphous reddish brown substance, which is for the most part insoluble in the ordinary reagents. The bark of the young twigs, as contrasted with older bark, shows an epidermal layer with a thick, yellowish cuticle, fewer stone cells in the pericycle, narrower inner bark, and fewer secretion cells.

Powdered Cinnamon is yellowish brown or reddish brown. It contains numerous single and 2- to 4-compound starch grains, the single grains from 5 to 25 μ in diameter; stone cells irregular in shape, occasionally with one wall much thinner than the other walls, sometimes containing starch; fibers from 300 to 1500 μ in length, with very thick, more or less wavy and slightly lignified walls; parenchyma cells with reddish brown walls; elongated secretion cells containing volatile oil or mucilage; phloem ray cells with minute needles of calcium oxalate; and fragments of somewhat lignified cork.

Foreign organic matter, page 886—The amount of foreign organic matter in Cinnamon does not exceed 2 percent.

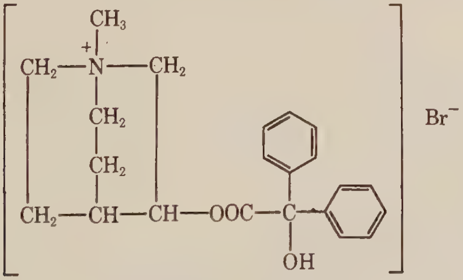
Assay—Place about 100 g. of Cinnamon, preferably coarsely comminuted, and accurately weighed, in the flask of the apparatus used for volatile oil determinations and proceed as directed on page 889, using the separator for oils heavier than water.

Packaging and storage—Preserve Cinnamon in well-closed containers, preferably in a cool, dry place.

Category—Flavor.

Citrate, Magnesium, Solution, page 399
Citrate, Potassium, page 571
Citrated Caffeine, page 111
Citrated Caffeine Tablets, page 112

Clidinium Bromide*



3-Hydroxy-1-methylquinuclidinium Bromide Benzilate

$C_{22}H_{26}BrNO_3$ Mol. wt. 432.36

Clidinium Bromide contains not less than 99.0 percent and not more than 100.5 percent of $C_{22}H_{26}BrNO_3$, calculated on the dried basis.

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* Patented. See notice, page ii.

Description—Clidinium Bromide occurs as a white or nearly white, almost odorless, crystalline powder. It is optically inactive.

Solubility—Clidinium Bromide is soluble in water and in alcohol. It is very slightly soluble in ether and in benzene.

Identification—

A: To a cold solution of 250 mg. of Clidinium Bromide in 5 ml. of water in an ice bath add 5 ml. of trinitrophenol T.S. and scratch the side of the tube with a glass rod to induce crystallization. Collect the precipitate on a filter, wash well with cold water, and dry at 105° for 1 hour: the picrate so obtained melts between 184° and 189°, page 814. (*Caution: Picrates may be explosive.*)

B: To a solution of 100 mg. of Clidinium Bromide in 2 ml. of water add a few drops of diluted nitric acid and 1 ml. of silver nitrate T.S.: a yellowish white precipitate is produced.

Melting range, page 814—Clidinium Bromide melts between 240° and 244°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Clidinium Bromide, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Clidinium Bromide Reference Standard, similarly measured.

Loss on drying, page 814—Dry Clidinium Bromide at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Clidinium Bromide yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Clidinium Bromide is 20 parts per million.

Limit of 3-quinuclidinyl benzilate and 3-hydroxy-1-methylquinuclidinium bromide—

Modified Dragendorff reagent—Dissolve 850 mg. of bismuth nitrate in a mixture of 10 ml. of glacial acetic acid and 40 ml. of water. Prepare another solution by dissolving 8 g. of potassium iodide in 20 ml. of water. Mix 5 ml. of each solution, dilute to 50 ml. with dilute sulfuric acid (1 in 10), and mix.

Standard preparation—Dissolve 100.0 mg. of NF Clidinium Bromide Reference Standard in 1.0 ml. of methanol.

Reference preparation A—Dissolve 10.0 mg. of NF 3-Hydroxy-1-methylquinuclidinium Bromide Reference Standard in 1.0 ml. of methanol. Add 50 µl. of this solution to 100.0 mg. of NF Clidinium Bromide Reference Standard dissolved in 1.0 ml. of methanol.

Reference preparation B—Dissolve 3.0 mg. of NF 3-Quinuclidinyl Benzilate Reference Standard in 100.0 ml. of methanol.

Test preparation—Dissolve 100.0 mg. of Clidinium Bromide in 1.0 ml. of methanol.

Solvent mixture—Mix 70 volumes of acetone, 20 volumes of methanol, 4 volumes of water, and 6 volumes of hydrochloric acid.

Chromatographic plates—Use suitable thin-layer chromatographic plates (see page 791) coated with a 0.25-mm. layer of silica gel G. Place the plates in a chromatographic chamber saturated with the *Solvent mixture,* and allow the solvent front to ascend about 15 cm. Remove the plates from the chamber, dry at 105° for 15 minutes, and cool.

Procedure for 3-quinuclidinyl benzilate—Apply 20 µl. each of the *Standard preparation,* of *Reference preparation B,* and of the *Test preparation* to separate points on one plate. Place the plate in an unsaturated chromatographic chamber containing fresh *Solvent mixture,* and allow the solvent front to ascend 10 cm. Remove the plate, dry at 105° for 10 minutes, cool, and spray with potassium iodoplatinate T.S.: clidinium bromide produces a spot at about R_f 0.5 and 3-quinuclidinyl benzilate produces a spot at about R_f 0.8; the *Test preparation* shows no spot of 3-quinuclidinyl benzilate.

Procedure for 3-hydroxy-1-methylquinuclidinium bromide—Apply 20 µl. each of *Reference preparation A* and of the *Test preparation* to separate points on another plate. Place the plate in an unsaturated chromatographic chamber containing fresh *Solvent mixture,* and allow the solvent front to ascend for 10 cm. Remove the plate, dry at 105° for 10 minutes, cool, and spray with *Modified Dragendorff reagent:* 3-hydroxy-1-methylquinuclidinium bromide produces a spot at about R_f 0.4; any spot from the *Test preparation* is not greater in size or intensity than the spot occurring at R_f 0.4 produced by the 3-hydroxy-1-methylquinuclidinium bromide in *Reference preparation A,* corresponding to not more than 0.5 percent.

Assay—Dissolve about 1.2 g. of Clidinium Bromide, accurately weighed, in 80 ml. of glacial acetic acid, warming if necessary to effect solution. Cool, add 15 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in dioxane, determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 43.24 mg. of $C_{22}H_{26}BrNO_3$.

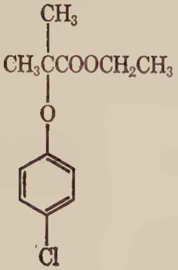
Packaging and storage—Preserve Clidinium Bromide in tight, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**2.5 mg.** three times a day.

USUAL DOSE RANGE—**2.5** to **5 mg.** three or four times a day.

Clofibrate*



Ethyl 2-(*p*-Chlorophenoxy)-2-methylpropionate

$C_{12}H_{15}ClO_3$ Mol. wt. 242.70

Clofibrate contains not less than 97.0 percent and not more than 103.0 percent of $C_{12}H_{15}ClO_3$, calculated on the anhydrous basis.

Description—Clofibrate occurs as a colorless to pale yellow liquid with a characteristic odor.

Solubility—Clofibrate is insoluble in water. It is soluble in acetone, in alcohol, in benzene, and in chloroform.

Infrared absorption, page 866—The infrared absorption spectrum, determined in a 0.1-cm. cell, of a 1 in 10 solution in carbon disulfide of Clofibrate, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Clofibrate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Clofibrate in methanol exhibits maxima and minima at the same wavelengths as that of NF Clofibrate Reference Standard, similarly measured.

Refractive index, page 858—The refractive index at 20° of Clofibrate is between 1.500 and 1.505.

Water, page 900—Determine the water content of Clofibrate by the titrimetric method: not more than 0.2 percent is found.

Acidity—Mix 10.0 g. of Clofibrate with 100 ml. of neutralized alcohol, add 3 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide: not more than 0.9 ml. is required for neutralization.

Limit of *p*-chlorophenol—

Standard preparation—Dissolve 50.0 mg. of *p*-chlorophenol in 500.0 ml. of 0.1 *N* sodium hydroxide. Dilute 4.0 ml. of this solution to 100.0 ml. with 0.1 *N* sodium hydroxide, and mix.

Test preparation—Transfer 2.0 g. of Clofibrate to a 250-ml. separator, and add 50 ml. of solvent hexane which has been previously washed with two 25-ml. portions of 0.1 *N* sodium hydroxide followed by successive quantities of water until the washings are no longer alkaline to phenolphthalein T.S. Dissolve the sample in the solvent hexane, and extract this solution successively with two 20-ml. portions and one 5-ml. portion of 0.1 *N* sodium hydroxide. Allow the phases to separate completely, and collect the aqueous phases in a 50-ml. volumetric flask, discarding the solvent hexane phase. Dilute the aqueous alkaline solution to volume with 0.1 *N* sodium hydroxide, and mix.

Test preparation blank—Prepare the solution as directed under *Test preparation*, omitting only the sample.

Procedure—Transfer 6.0 ml. of the *Standard preparation* to a 250-ml. separator, and dilute to 20 ml. with 0.1 *N* sodium hydroxide. To a second 250-ml. separator transfer 20.0 ml. of 0.1 *N* sodium hydroxide to serve as the *Standard preparation blank*. To the third and fourth 250-ml. separators transfer 20.0 ml. of the *Test preparation* and of the *Test preparation blank*, respectively. To each separator add 20.0 ml. of a buffer solution prepared by dissolving 24.736 g. of boric acid in sufficient 0.1 *N* sodium hydroxide to make 1000 ml. Add successively 0.1 ml. of 4-aminoantipyrine solution (3 in 100) and 0.2 ml. of potassium ferricyanide solution (1 in 10) to each separator, shaking well after each addition. Allow the mixtures to stand for 3 minutes, add 10 ml. of chloroform to each separator, and shake well. Allow the layers to separate completely, and transfer the chloroform layer from each separator to separate 25-ml. volumetric flasks. Wash the contents remaining in each separator with 2 ml. of chloroform without shaking, and add the chloroform washings to the respective volumetric flasks. Add 5 ml. of chloroform to each separator, and shake well. Allow the layers to separate, and add the chloroform layer from each separator to the contents of the respective volumetric flasks. Finally, wash the contents in each of the separators with 3 ml. of chloroform adding the chloroform washings to the contents in the respective volumetric flasks. Dilute each volumetric flask to volume with chloroform, add about 0.5 g. of anhydrous sodium sulfate, shake, and allow to stand for 5 minutes. Concomitantly determine the absorbances of the solutions in 5-cm. cells, at the maximum at about 455 mμ, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the solution from the *Standard preparation* as A_1, from the *Standard preparation blank* as A_2, from the *Test preparation* as A_3, and from the *Test preparation blank* as A_4. The corrected absorbance of the solution from the *Test preparation* $(A_3 - A_4)$ is not greater than the corrected absorbance of the solution from the *Standard preparation* $(A_1 - A_2)$, corresponding to not more than 30 parts per million of *p*-chlorophenol.

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* Patented. See notice, page ii.

Assay—

Ion-exchange resin—Allow about 3 g. of a strongly basic polystyrene anion-exchange resin to stand for about 15 minutes, with occasional stirring, in a beaker containing 75 ml. of 1 *N* sodium hydroxide. Wash the resin with water until the washings are neutral to litmus paper, then wash with three 50-ml. portions of methanol.

Ion-exchange column—Place a plug of glass wool in the base of a 1 × 15-cm. ion-exchange tube, and transfer to the tube a sufficient amount of *Ion-exchange resin*, slurried in methanol, to produce a column bed height of from 6 to 8 cm.

Standard preparation—Transfer about 50 mg. of NF Clofibrate Reference Standard, accurately weighed, to a 50-ml. volumetric flask, add methanol to volume, and mix. Transfer 20.0 ml. of the solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with methanol, and mix.

Assay preparation—Transfer about 200 mg. of Clofibrate, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 10.0 ml. of this solution to the *Ion-exchange column*, and collect the eluate in a 100-ml. volumetric flask. Rinse the column with 25 ml. of methanol, collect the rinsings in the volumetric flask, dilute to volume with methanol, and mix. Transfer 5.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with methanol, and mix.

Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum occurring at about 226 mμ, with a suitable spectrophotometer, using methanol as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{12}H_{15}ClO_3$ in the Clofibrate taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Clofibrate in tight, light-resistant containers.

CATEGORY—Anticholesterolemic.

USUAL DOSE—**500 mg.** four times daily.

Clofibrate Capsules

Clofibrate Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{12}H_{15}ClO_3$.

Identification—A portion of the contents of Clofibrate Capsules responds to the *Infrared absorption test* under *Clofibrate*, page 173.

Weight variation, page 901—Clofibrate Capsules meet the requirements of the weight variation test for capsules.

Assay—Weigh the contents of not less than 20 Clofibrate Capsules, and determine the average weight per capsule. Mix the combined contents well, and proceed as directed in the *Assay* under *Clofibrate*, page 173. Calculate the quantity, in mg., of $C_{12}H_{15}ClO_3$ in the portion of the Capsules taken, by the formula $10C \times (A_U/A_S)$.

Packaging and storage—Preserve Clofibrate Capsules in well-closed, light-resistant containers.

Capsules available—Clofibrate Capsules usually available contain the following amounts of clofibrate: 250 and 500 mg.

CATEGORY and DOSE—See Clofibrate.

Cobalamin Concentrate

Cobalamin Concentrate consists of the dried, partially purified product resulting from the growth of selected *Streptomyces* cultures or other cobalamin-producing microorganisms. It may contain harmless diluents and stabilizing agents. Cobalamin Concentrate contains, in each g., not less than 500 mcg. of cobalamin.

Description—Cobalamin Concentrate occurs as pink to brown granules or fine powder.

Identification—Ignite 1 g. of Cobalamin Concentrate at a temperature not exceeding 500°. If necessary, nitric acid may be added to destroy the organic matter, but sulfuric acid is not to be used. Dissolve the residue in 5 ml. of hydrochloric acid, transfer the solution to a 25-ml. graduate, add 1 ml. of stannous chloride solution (1 in 10), and dilute to 10 ml. Then add 2.5 ml. of potassium thiocyanate solution (1 in 2) and 12.5 ml. of acetone, and mix well: a bluish green color forms (cobalt).

Loss on drying, page 814—Dry Cobalamin Concentrate at 60° under a pressure of not more than 5 mm. of mercury for 2 hours: it loses not more than 5 percent of its weight.

pH, page 824—The pH of a solution of Cobalamin Concentrate (1 in 200) is between 4.0 and 8.0.

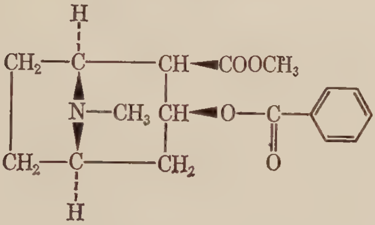
Assay—Proceed as directed under *Cobalamin Assay,* page 793.

Packaging and storage—Preserve Cobalamin Concentrate in tight containers, protected from light.

Labeling—The potency in terms of the number of mcg. of cobalamin in each g. of Cobalamin Concentrate must be stated on the label.

CATEGORY—Vitamin B_{12} supplement.

Cocaine



Methyl 3β-Hydroxy-1αH,5αH-tropane-2β-carboxylate Benzoate (Ester)

$C_{17}H_{21}NO_4$ Mol. wt. 303.36

Cocaine, dried over phosphorus pentoxide for 3 hours, contains not less than 99.0 percent and not more than 101.0 percent of $C_{17}H_{21}NO_4$.

Description—Cocaine occurs as colorless to white crystals, or as a white, crystalline powder. A solution of Cocaine in diluted hydrochloric acid is levorotatory. Its saturated solution is alkaline to litmus.

Solubility—Cocaine is slightly soluble in water, is freely soluble in alcohol, in chloroform, in ether, and is soluble in olive oil. It is sparingly soluble in mineral oil, and is very soluble in warm alcohol.

Identification—

A: Heat about 100 mg. of powdered Cocaine with 1 ml. of sulfuric acid at 100° for 5 minutes, then cautiously mix with 2 ml. of water: the mixture has the aromatic odor of methyl benzoate and, upon cooling, yields crystals of benzoic acid.

B: Dissolve 100 mg. of Cocaine in 0.4 ml. of 1 *N* hydrochloric acid and enough water to make 5 ml., and add 5 drops of a solution of chromium trioxide (1 in 20): a yellow precipitate is produced which redissolves on shaking the mixture. Add 1 ml. of hydrochloric acid: a permanent, orange-colored, crystalline precipitate is formed.

C: Dissolve 10 mg. of Cocaine in 1 ml. of 0.02 *N* hydrochloric acid, and evaporate the solution just to dryness on a steam bath. Dissolve the residue in 2 drops of water, and add 1 ml. of 0.1 *N* potassium permanganate: a violet, crystalline precipitate forms, which appears brownish violet when collected on a filter, and shows characteristic violet-red crystalline aggregates under the low power of a microscope.

Melting range, page 814—Cocaine melts between 96° and 98°.

Loss on drying, page 814—Dry Cocaine over phosphorus pentoxide for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Cocaine yields not more than 0.1 percent of residue on ignition.

Readily carbonizable substances, page 856—Dissolve 500 mg. of Cocaine in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid A.

Cinnamyl-cocaine and other reducing substances—Dissolve 300 mg. of finely powdered Cocaine in 1 ml. of 1 *N* hydrochloric acid with the aid of heat, if necessary, and dilute with water to 15 ml. Mix 5 ml. of this solution with 0.3 ml. of 1 *N* sulfuric acid and 0.1 ml. of 0.1 *N* potassium permanganate: the violet color does not disappear entirely within 30 minutes.

Isoatropyl-cocaine—Dilute in a beaker 5 ml. of the solution of Cocaine prepared in the test for *Cinnamyl-cocaine and other reducing substances* with 80 ml. of water, add 0.2 ml. of ammonia T.S., and stir the solution vigorously during 5 minutes, occasionally rubbing the inner wall of the beaker with a stirring rod: a crystalline precipitate of cocaine develops, and the supernatant liquid is clear.

Assay—Dissolve about 600 mg. of Cocaine, previously dried over phosphorus pentoxide for 3 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 30.34 mg. of $C_{17}H_{21}NO_4$.

Packaging and storage—Preserve Cocaine in well-closed, light-resistant containers.

CATEGORY—Local anesthetic (narcotic).

APPLICATION—Topical to mucous membrane as a 1 percent solution.

Cocaine Hydrochloride Tablets

Cocaine Hydrochloride Tablets contain not less than 91.0 percent and not more than 109.0 percent of the labeled amount of $C_{17}H_{21}NO_4.HCl$.

Identification—

A: Add 5 drops of a solution of chromium trioxide (1 in 20) to 5 ml. of a filtered solution of Cocaine Hydrochloride Tablets, equivalent to cocaine hydrochloride 1 in 50: a yellow precipitate is formed which redissolves when the mixture is shaken. On the addition of 1 ml. of hydrochloric acid, a permanent, yellowish orange, crystalline precipitate is formed.

B: Dissolve a portion of powdered Cocaine Hydrochloride Tablets, equivalent to about 10 mg. of cocaine hydrochloride, in 1 ml. of water, filter, and add 2 ml. of 0.1 *N* potassium permanganate: a red-purple, crystalline precipitate is produced which appears brown when collected on a filter, and shows characteristic, crystalline aggregates under the low power of a microscope.

C: Add silver nitrate T.S., dropwise, to a filtered solution of Cocaine Hydrochloride Tablets, equivalent to cocaine hydrochloride 1 in 20: a white precipitate forms which is insoluble in nitric acid.

Disintegration, page 878—The disintegration time limit for Cocaine Hydrochloride Tablets is 15 minutes.

Content uniformity, *Method II,* page 798—Cocaine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets using the following special procedure: Transfer one tablet to a 100-ml. volumetric flask containing 50 ml. of water, and shake the flask until the tablet is dissolved. Dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate, if necessary, with water to provide a solution containing approximately 80 mcg. of cocaine hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a standard solution of USP Cocaine Hydrochloride, in the same medium, at a concentration of about 80 mcg. per ml., in 1-cm. cells, at the maximum at about 275 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{17}H_{21}NO_4.HCl$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of cocaine hydrochloride in the tablet; D is the exact concentration, in mcg. per ml., of cocaine hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the standard solution.

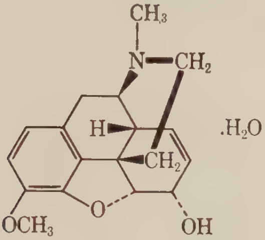
Assay—Weigh and finely powder not less than 20 Cocaine Hydrochloride Tablets. Dissolve an accurately weighed portion of the powder, equivalent to about 60 mg. of cocaine hydrochloride, in 10 ml. of water. Render the solution slightly alkaline with ammonia T.S., and completely extract the cocaine with small successive portions of ether. Evaporate the combined ether extracts to one-half their volume on a steam bath, transfer the remaining liquid to a separator, and wash it with three 5-ml. portions of water. Shake the water washings with a small portion of ether and add the ether washing to the combined ether extracts. Add 10.0 ml. of 0.05 *N* sulfuric acid to the ether solution, agitate the mixture thoroughly, and draw off the acidified water layer into a beaker. Again wash the ether with 2 small portions of water, add the washings to the acid liquid, and titrate the excess acid with 0.02 *N* sodium hydroxide, using methyl red T.S. as the indicator. Each ml. of 0.05 *N* sulfuric acid is equivalent to 16.99 mg. of $C_{17}H_{21}NO_4 . HCl$.

Packaging and storage—Preserve Cocaine Hydrochloride Tablets in well-closed, light-resistant containers.

Tablets available—Cocaine Hydrochloride Tablets usually available contain the following amounts of cocaine hydrochloride: 8 and 15 mg.

CATEGORY—Local anesthetic (narcotic)

Codeine



7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol

$C_{18}H_{21}NO_3 . H_2O$ Mol. wt. 317.39

Codeine, dried at 80° for 4 hours, contains not less than 98.5 percent and not more than 100.5 percent of $C_{18}H_{21}NO_3$.

Description—Codeine occurs as colorless or white crystals, or as a white, crystalline powder. It effloresces slowly in dry air and is affected by light. In acid or alcohol solutions it is levorotatory. A saturated solution of Codeine is alkaline to litmus.

Solubility—Codeine is slightly soluble in water, is freely soluble in alcohol, and is very soluble in chloroform. It is sparingly soluble in ether. When heated in an amount of water insufficient for complete solution, Codeine melts to oily drops which crystallize on cooling.

Identification—

A: Add 0.5 ml. of sulfuric acid, containing 5 mg. of selenious acid in each ml., to 1 mg. of Codeine contained in a porcelain crucible or small dish: a green color is produced, which changes rapidly to blue, then slowly back to green.

B: Dissolve about 10 mg. of Codeine in 5 ml. of sulfuric acid, add a drop of ferric chloride T.S., and warm the mixture: the solution becomes blue, but changes to reddish brown on the addition of 1 drop of nitric acid.

C: To 1 mg. of Codeine contained in a porcelain crucible or small dish add 0.5 ml. of sulfuric acid-formaldehyde T.S.: an intense violet-blue color is produced at once.

D: Add 2 drops of nitric acid to about 2 mg. of Codeine: a light orange color is produced, fading to greenish yellow within one minute (*difference from morphine*).

E: Dissolve about 5 mg. of Codeine in about 5 ml. of diluted sulfuric acid and add several drops of potassium ferricyanide T.S., containing 1 drop of ferric chloride T.S. in each ml.: a light greenish yellow color is produced (*difference from morphine*).

Melting range, page 814—Codeine, rendered anhydrous by drying at 80° for 4 hours, melts, within a range of 2°, between 154° and 158°.

Loss on drying, page 814—Dry Codeine at 80° for 4 hours: it loses not more than 6 percent of its weight.

Residue on ignition, page 858—Codeine yields not more than 0.1 percent of residue on ignition.

Readily carbonizable substances, page 856—Dissolve 10 mg. of Codeine in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid S.

Morphine—Dissolve about 50 mg. of potassium ferricyanide in 10 ml. of water, and add 1 drop of ferric chloride T.S. and 1 ml. of a neutral or slightly acid solution of Codeine (1 in 100) made with the aid of sulfuric acid: no blue color is produced immediately.

Assay—Dissolve about 400 mg. of Codeine, previously dried at 80° for 4 hours and accurately weighed, by warming it in 30.0 ml. of 0.1 *N* sulfuric acid. Cool, and add 10 ml. of water. Add 3 drops of methyl red T.S., and titrate the excess acid with 0.1 *N* sodium hydroxide. Each ml. of 0.1 *N* sulfuric acid is equivalent to 29.94 mg. of $C_{18}H_{21}NO_3$.

Packaging and storage—Preserve Codeine in tight, light-resistant containers.

CATEGORY—Analgesic (narcotic); antitussive.

USUAL DOSE—Analgesic, **30 mg.** every four hours; antitussive **5 to 10 mg.** every 4 hours.

USUAL DOSE RANGE—Analgesic, **15 to 60 mg.**

Codeine and Terpin Hydrate Elixir, page 685

Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets

Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{21}NO_3 . H_3PO_4 . {}^1/_2H_2O$ (codeine phosphate), and not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_9H_8O_4$ (aspirin), of $C_{10}H_{13}NO_2$ (phenacetin), and of $C_8H_{10}N_4O_2$ (caffeine).

Identification—

A: Transfer a quantity of finely powdered Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets, equivalent to about 1 mg. of codeine phosphate, to a test tube, and add a few drops of sulfuric acid containing 5 mg. of selenious acid in each ml.: a green color is produced which rapidly changes to blue (*presence of codeine*).

B: Mix a portion of finely powdered Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets, equivalent to about 10 mg. of codeine phosphate, with 10 ml. of water, and filter: the filtrate, when neutralized with ammonia T.S., responds to the tests for *Phosphate*, page 809.

C: Crush a Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablet, and boil it with 5 ml. of diluted sulfuric acid: acetic acid, recognizable by its odor, is evolved. Cool the mixture, and add a few drops of ferric chloride T.S.: a violet to purple color is produced (*presence of aspirin*).

D: Crush a Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablet, and boil for a few minutes with 3 ml. of diluted hydrochloric acid. Dilute with 10 ml. of water, cool, filter, and add 1 drop of potassium dichromate T.S. to the filtrate: the mixture slowly develops a ruby-red color (*presence of phenacetin*).

E: Crush a Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablet, shake with 5 ml. of water, filter, and to the filtrate add a few drops of tannic acid T.S.: a precipitate is produced which is soluble in an excess of the reagent (*presence of caffeine*).

Disintegration, page 878—The disintegration time limit for Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets is 10 minutes.

Content uniformity, *Method I*, page 799—Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets meet the requirements of the content uniformity test for tablets when tested for codeine phosphate and for caffeine content.

Free salicylic acid—

Ferric chloride-urea reagent—Dissolve by swirling, without the aid of heat, 60 g. of urea in a mixture of 8 ml. of ferric chloride solution (6 in 10) and 42 ml. of 0.05 *N* hydrochloric acid. Adjust the resulting solution to a pH of 3.2, if necessary, by the addition of 6 *N* hydrochloric acid.

Standard preparation—Transfer 75.0 mg. of salicylic acid, previously dried over silica gel for 3 hours and accurately weighed, to a 100-ml. volumetric flask, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this last solution to a 50-ml. volumetric flask containing 10 ml. of methanol, 2 drops of hydrochloric acid, and 10 ml. of a 1 in 10 solution of glacial acetic acid in ether, dilute to volume with chloroform, and mix.

Test preparation—Pack a pledget of glass wool in the base of a 20 × 2.5-cm. chromatographic tube, and uniformly pack the tube with a mixture of 3 g. of chromatographic siliceous earth and 2 ml. of freshly prepared *Ferric chloride-urea reagent.* Weigh accurately a quantity of finely powdered Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets, equivalent to 100 mg. of aspirin, mix with 10 ml. of chloroform by stirring for 3 minutes, and then transfer to the chromatographic column with the aid of a few ml. of chloroform. Pass 50 ml. of chloroform through the column, rinse the tip of the chromatographic tube with chloroform, and discard the eluate. Prepare as a receiver a 50-ml. volumetric flask containing 10 ml. of methanol and 2 drops of hydrochloric acid, and elute any salicylic acid from the column by passing 10 ml. of a 1 in 10 solution of glacial acetic acid in ether that has been recently saturated with water, followed by 30 ml. of chloroform. Dilute the eluate to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 306 mμ, with a suitable spectrophotometer, using as the blank a solvent mixture of the same composition as that used for the *Standard preparation:* the absorbance of the *Test preparation* does not exceed that of the *Standard preparation* (0.75 percent, calculated on the labeled aspirin content).

Assay for codeine phosphate—

Internal standard solution—Prepare a

solution in chloroform containing 400 mcg. of USP Propoxyphene Hydrochloride Reference Standard in each ml.

Standard preparation—Transfer about 30 mg. of USP Codeine Phosphate, accurately weighed, to a 125-ml. separator, add 20 ml. of sodium hydroxide T.S., swirl to mix, and continue as directed under *Assay preparation*, beginning with "... and extract the solution with four 25-ml. portions of methylene chloride. ..." Use the final solution as directed in the *Procedure*.

Assay preparation—Weigh and finely powder not less than 20 Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 30 mg. of codeine phosphate, to a 125-ml. separator, add 20 ml. of sodium hydroxide T.S., swirl to mix, and extract the solution with four 25-ml. portions of methylene chloride, filtering each extract through anhydrous sodium sulfate into a 150-ml. beaker. Evaporate the combined extracts to a volume of about 5 ml. on a steam bath with the aid of a current of air, and quantitatively transfer the residual liquid to a glass-stoppered 25-ml. conical flask with the aid of 20 ml. of methylene chloride. Evaporate to near dryness on a steam bath, and complete the evaporation to dryness with the aid of a current of air, without heating. Dissolve the residue in 10.0 ml. of *Internal standard solution*, and use the resultant solution as directed in the *Procedure*.

Procedure—Inject a portion of the *Standard preparation* into a suitable gas chromatograph equipped with a flame-ionization detector, and record the chromatogram. Under typical conditions, the instrument contains a 1-meter × 6-mm. (outside diameter) glass column packed with 3 to 5 percent methyl silicone gum on 80 to 100-mesh or 100 to 120-mesh acid-washed, silanized, flux-calcined siliceous earth. The column is maintained at 215°, and the injector port and detector block at 230°; helium is used as the carrier gas at a flow rate of 50 ml. per minute.

Measure the peak height of each component, recording the height of the propoxyphene hydrochloride peak as P_1 and that of the codeine phosphate peak as P_2.

Similarly, inject a portion of the *Assay preparation* into the chromatograph, and record the chromatogram under the same conditions as described for the *Standard preparation*. Measure the peak height of each component, recording the height of the propoxyphene hydrochloride peak as p_1 and that of the codeine phosphate peak as p_2.

Calculate the quantity, in mg., of $C_{18}H_{21}NO_3 . H_3PO_4 . {}^1/_2H_2O$ in the portion of Tablets taken by the formula $10C \times (p_2 \times P_1)/(p_1 \times P_2)$, in which C is the exact equivalent concentration, in mg. per ml., of codeine phosphate in the *Standard preparation*.

Assay for aspirin, phenacetin, and caffeine—

Preparation of chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 200-mm. test tube to which is fused a 5-cm. length of 6 or 8-mm. tubing) with the aid of a tamping rod of stainless steel, aluminum, or glass, at least 30 cm. long and having a disk with a diameter about 1 mm. less than that of the chromatographic tube. To 2.0 g. of purified siliceous earth (see page 927) in a glass mortar add 2.0 ml. of approximately 4 *N* sulfuric acid and incorporate by kneading thoroughly with a flexible spatula blade until the mixture is fluffy. Transfer to the column and tamp gently to compress the material to a uniform mass. In like manner, mix intimately 2.0 g. of purified siliceous earth with 2.0 ml. of approximately 1 *N* sodium bicarbonate, transfer to the column, and gently compress with the tamping rod. Wash the column so prepared with one 20-ml. portion of water-washed ether and discard the washings.

Phenacetin standard solution—Transfer to a 100-ml. volumetric flask about 50 mg. of USP Phenacetin Reference Standard, previously dried at 60° for 1 hour and accurately weighed, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, add isooctane to volume, and mix.

Aspirin standard solution—Transfer to a 100-ml. volumetric flask about 50 mg. of USP Aspirin Reference Standard, previously recrystallized from isopropanol, dried over silica gel for 5 hours, and accurately weighed. Add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, add 1 ml. of glacial acetic acid, dilute to volume with chloroform, and mix. Use within 3.5 hours.

Caffeine standard solution—Transfer to a 100-ml. volumetric flask about 100 mg. of NF Caffeine Reference Standard, previously dried at 80° for 4 hours and accurately weighed, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparation—Weigh and finely powder not less than 20 Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets. Transfer to a 50-ml. volumetric flask an accurately weighed portion of the powder, equivalent to about 50 mg. of aspirin, add 30 ml. of chloroform, and mix thoroughly by shaking. Add 0.1 ml. of glacial acetic acid, dilute to volume with chloroform, and mix.

Procedure—(Use water-washed solvents.) Dilute 5.0 ml. of the *Assay preparation* with 20 ml. of ether and pass the solution into the column without pressure. After all of the solution has passed into the column, complete the elution of the phenacetin from the column with five 5-ml. portions of ether, allowing each portion to pass into the column before the next portion is added, and collecting the total ether eluate in a glass evaporating dish. Immediately after the last portion of ether has passed through the column, rinse the tip of the outlet tube with chloroform, collecting the rinsings in the evaporating dish, remove the dish, and replace it with a 50-ml. volumetric flask to receive the caffeine eluate in the next step. Evaporate the total eluate to dryness on a steam bath in a current of air. Dissolve the residue in 5 ml. of chloroform, transfer to a 50-ml. volumetric flask, dilute to volume with isooctane, and mix.

To elute the caffeine, pass 48 ml. of chloroform through the column, rinse the tip with chloroform, add sufficient chloroform to make 50.0 ml., and mix. Replace the receiver with a 100-ml. volumetric flask, and elute the aspirin with a solution of 0.5 ml. of glacial acetic acid in 5 ml. of chloroform, followed by 90 ml. of a solution of glacial acetic acid in chloroform (1 in 100), dilute to volume with the latter solvent, and mix. The absorbance of the aspirin solution must be determined within 3.5 hours after preparation of the *Assay preparation.*

Determine the absorbance of each solution in 1-cm. cells, with a suitable spectrophotometer, at 285 mμ for the phenacetin solution, at 276 mμ for the caffeine solution, and at 280 and 310 mμ for the aspirin solution, using as a blank the respective solvent employed for each solution. Record the absorbance of each *Standard solution* as A_S and that of the corresponding *Assay solution* as A_U.

Calculation for phenacetin—Calculate the quantity, in mg., of $C_{10}H_{13}NO_2$ per tablet by the formula $0.5C \times (A_U/A_S) \times$ (Av. Wt. per Tablet/Wt. of Sample), in which C is the exact quantity, in mcg., of phenacetin per ml. of the *Phenacetin standard solution.*

Calculation for aspirin—Calculate the quantity, in mg., of $C_9H_8O_4$ per tablet by the formula $C \times [(A_{U280} - 0.2A_{U310})/A_{S280}] \times$ (Av. Wt. per Tablet/Wt. of Sample), in which C is the exact quantity, in mcg., of aspirin per ml. of the *Aspirin standard solution* and A_U and A_S are the absorbances of the sample solution and standard solution, respectively, at the wavelengths indicated by the subscripts.

Calculation for caffeine—Calculate the quantity, in mg., of $C_8H_{10}N_4O_2$ per tablet by the formula $0.5C \times (A_U/A_S) \times$ (Av. Wt. per Tablet/Wt. of Sample), in which C is the exact quantity, in mcg., of caffeine per ml. of the *Caffeine standard solution.*

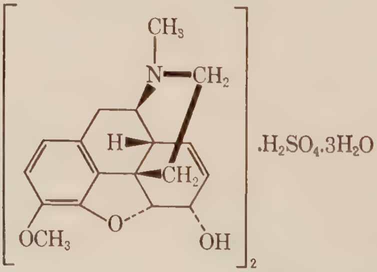
Packaging and storage—Preserve Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets in well-closed containers.

Tablets available—Codeine Phosphate, Aspirin, Phenacetin, and Caffeine Tablets usually available contain the following amounts of codeine phosphate: 8, 15, 30, and 60 mg.; of aspirin: 230 mg.; of phenacetin: 150 mg.; and of caffeine: 30 mg.

CATEGORY—Analgesic (narcotic).

USUAL DOSE OF CODEINE PHOSPHATE—**8** to **60 mg.**; OF ASPIRIN—**600 mg.**; OF PHENACETIN—**300 mg.**; OF CAFFEINE—**200 mg.**

Codeine Sulfate



7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol Sulfate (2:1)

$(C_{18}H_{21}NO_3)_2 . H_2SO_4 . 3H_2O$ Mol. wt. 750.87

Codeine Sulfate, dried at 105° for 3 hours, contains not less than 98.5 percent and not more than 100.5 percent of $(C_{18}H_{21}NO_3)_2 . H_2SO_4$.

Description—Codeine Sulfate occurs as white crystals, usually needle-like, or as a white, crystalline powder. It is affected by light.

Solubility—Codeine Sulfate is soluble in water, and is very slightly soluble in alcohol. It is freely soluble in water at 80°. It is insoluble in chloroform and in ether.

Identification—

A: To 1 mg. of Codeine Sulfate contained in a porcelain crucible or small dish add 0.5 ml. of sulfuric acid-formaldehyde T.S.: an intense violet-blue color is produced at once (*difference from morphine which gives an intense purple color*).

B: To 1 mg. of Codeine Sulfate contained in a porcelain crucible or small dish add 0.5 ml. of sulfuric acid containing in each ml. 5 mg. of selenious acid: a green color is produced at once, which rapidly changes to blue, then slowly to dark olive-green (*difference from morphine which gives at once a blue color, changing to green*).

C: To a solution of 5 mg. of Codeine Sulfate in 5 ml. of sulfuric acid contained in a test tube, add 1 drop of ferric chloride T.S., mix, and heat in boiling water for 2 minutes: a blue color is produced which upon the addition of a drop of nitric acid changes to dark red-brown (*ethylmorphine and morphine give the same color reactions, but hydromorphone and papaverine do not*).

D: Codeine Sulfate responds to the tests for *Sulfate*, page 810.

Specific rotation, page 822—The specific rotation of Codeine Sulfate, calculated on the dried basis, determined in a solution containing the equivalent of 2 g. of Codeine Sulfate in each 100 ml., is between $-112.5°$ and $-115°$.

Acidity—Dissolve 500 mg. of Codeine Sulfate in 15 ml. of water, add 1 drop of methyl red T.S., and titrate with 0.02 *N* sodium hydroxide: not more than 0.3 ml. is required for neutralization.

Loss on drying, page 814—Dry Codeine Sulfate at 105° for 3 hours: it loses not less than 6 percent and not more than 7.5 percent of its weight.

Residue on ignition, page 858—Codeine Sulfate yields not more than 0.1 per cent of residue on ignition.

Readily carbonizable substances, page 856—Dissolve 10 mg. of Codeine Sulfate in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid S.

Morphine—Dissolve about 50 mg. of potassium ferricyanide in 10 ml. of water, and add 1 drop of ferric chloride T.S. and 1 ml. of a solution of Codeine Sulfate (1 in 100): no blue color is produced immediately.

Assay—Dissolve about 1.4 g. of Codeine Sulfate, previously dried at 105° for 3 hours and accurately weighed, in 50 ml. of glacial acetic acid, warming if necessary to effect solution. Titrate with 0.1 *N* perchloric acid in glacial acetic acid determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 69.68 mg. of $(C_{18}H_{21}NO_3)_2.H_2SO_4$.

Packaging and storage—Preserve Codeine Sulfate in tight, light-resistant containers.

CATEGORY—Analgesic (narcotic); antitussive.

USUAL DOSE—Analgesic, **30 mg.** every 4 hours. Antitussive, **5** to **10 mg.** every 4 hours.

USUAL DOSE RANGE—Analgesic, **15** to **60 mg.**

Codeine Sulfate Tablets

Codeine Sulfate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $(C_{18}H_{21}NO_3)_2.H_2SO_4.3H_2O$.

Identification—

A: Digest a quantity of finely powdered Codeine Sulfate Tablets, equivalent to about 50 mg. of codeine sulfate, with 15 ml. of water and 5 ml. of diluted sulfuric acid for 1 hour. Filter, if necessary, and wash any undissolved residue with a few ml. of water. Render the filtrate alkaline with ammonia T.S., extract with several small portions of chloroform, and evaporate the chloroform solution to dryness on a steam bath. The resulting residue of codeine responds to *Identification tests A, B, and C* under *Codeine Sulfate*, page 180.

B: A filtered solution of Codeine Sulfate Tablets responds to the tests for *Sulfate*, page 810.

Disintegration, page 878—The disintegration time limit for Codeine Sulfate Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Codeine Sulfate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 25-ml. volumetric flask. Add 15 ml. of water, and shake to dissolve. Dilute to volume with water, and filter, discarding the first few ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with 0.01 *N* sodium hydroxide to provide a solution containing approximately 120 mcg. of codeine sulfate (trihydrate) per ml. Concomitantly determine the absorbance of this solution and of a standard solution of NF Codeine Sulfate, in the same medium, at a concentration of about 120 mcg. per ml., in 1-cm. cells, at the maximum at about 284 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity in mg., of $(C_{18}H_{21}NO_3)_2.H_2SO_4.3H_2O$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of codeine sulfate, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of codeine sulfate in the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the standard solution, in mcg. per ml., A_U is the absorbance of the tablet extract, and A_S is the absorbance of the standard solution.

Assay—Weigh and finely powder not less than 20 Codeine Sulfate Tablets. Weigh accurately a portion of the powder, equivalent to about 150 mg. of codeine sulfate, and transfer it completely to a 100-ml. volumetric flask. Add sufficient water to make a thin suspension, then add 20 ml. of 0.5 *N* sulfuric acid, shake the mixture occasionally during 2 hours, and allow it to stand overnight. Dilute to volume with water, mix, and filter through a filtering crucible. Transfer to a separator an accurately measured portion of the filtrate, equivalent to not less than 75 mg. of codeine sulfate, render the solution alkaline with ammonia T.S., and completely extract the alkaloid with successive 15-ml. portions of chloroform. Evaporate the combined chloroform solution nearly to dryness on a steam bath, add 25.0 ml. of 0.02 *N* sulfuric acid, and heat gently to dissolve the codeine and expel all of the chloroform. Cool, add 3 drops of methyl red T.S., and titrate the excess acid with 0.02 *N* sodium hydroxide. Each ml. of 0.02 *N* sulfuric acid is equivalent to 7.509 mg. of $(C_{18}H_{21}NO_3)_2.H_2SO_4.3H_2O$.

Packaging and storage—Preserve Codeine Sulfate Tablets in well-closed containers.

Tablets available—Codeine Sulfate Tablets usually available contain the following amounts of codeine sulfate: 15, 30, and 60 mg.

CATEGORY and DOSE—See Codeine Sulfate.

Cod Liver Oil

Cod Liver Oil is the partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linné and other species of the Family *Gadidæ*. Cod Liver Oil contains, in each g., not less than 255 mcg. (850 USP Units) of vitamin A and not less than 2.125 mcg. (85 USP Units) of vitamin D.

Cod Liver Oil may be flavored by the addition of not more than 1 percent of a suitable flavoring substance or a mixture of such substances.

Description—Cod Liver Oil is a thin, oily liquid, having a characteristic, slightly fishy but not a rancid odor, and a fishy taste.

Solubility—Cod Liver Oil is slightly soluble in alcohol. It is freely soluble in ether, in chloroform, in carbon disulfide, and in ethyl acetate.

Identification for vitamin A—To 1 ml. of a chloroform solution of Cod Liver Oil (1 in 40) add 10 ml. of antimony trichloride T.S.: a blue color results immediately.

Specific gravity, page 866—The specific gravity of Cod Liver Oil is not less than 0.918 and not more than 0.927.

Color—When viewed transversely in a tall, cylindrical, standard oil-sample bottle of colorless glass of about 120-ml. capacity, the color of Cod Liver Oil is not more intense than that of a mixture of 11 ml. of cobaltous chloride C.S., 76 ml. of ferric chloride C.S., and 33 ml. of water, in a similar bottle of the same internal diameter.

Nondestearinated cod liver oil—Fill a tall, cylindrical, standard oil-sample bottle of about 120-ml. capacity with Cod Liver Oil at a temperature between 23° and 28°, stopper, and immerse the bottle in a mixture of ice and water for 3 hours: the oil remains clear and does not deposit stearin.

Unsaponifiable matter, page 803—Cod Liver Oil contains not more than 1.3 percent of unsaponifiable matter.

Acid value—Mix 15 ml. of alcohol with 15 ml. of ether, add 5 drops of phenolphthalein T.S., and neutralize with 0.1 *N* sodium hydroxide. Dissolve 2 g. of Cod Liver Oil, accurately weighed, in the mixture, and boil the oil solution gently under a reflux condenser for 10 minutes. Cool, and titrate the mixture with 0.1 *N* sodium hydroxide to the production of a pink color which persists after shaking for 30 seconds: not more than 1 ml. of 0.1 *N* sodium hydroxide is required.

Iodine value, page 804—The iodine value of Cod Liver Oil is not less than 145 and not more than 180.

Saponification value, page 805—The saponification value of Cod Liver Oil is not less than 180 and not more than 192. If carbon dioxide has been used as a preservative, expose the Oil in a shallow dish in a vacuum desiccator for 24 hours before weighing the sample for determination of the saponification value.

Assay for vitamin A—Using an accurately weighed sample of 0.5 to 1 g. of Cod Liver Oil, proceed as directed under *Vitamin A Assay,* page 891.

Assay for vitamin D—Proceed as directed under *Vitamin D Assay, Biological Method,* page 895.

Packaging and storage—Preserve Cod Liver Oil in tight containers. It may be bottled or packaged in containers from which air has been expelled by the production of a vacuum or by an inert gas.

Labeling—The vitamin A potency and vitamin D potency of Cod Liver Oil, when designated on the label, are expressed in United States Pharmacopeia Units per g. of oil. These units may be referred to as USP Units.

CATEGORY—Source of vitamin A and D.

USUAL DOSE—**5 ml.** containing 1170 mcg. (3900 USP Units) of vitamin A and 9.7 mcg. (386 USP Units) of vitamin D.

NOTE: Cod Liver Oil containing more than the minimum NF requirements for both vitamin A and vitamin D may be administered in proportionally smaller doses.

Nondestearinated Cod Liver Oil

Nondestearinated Cod Liver Oil is the entire fixed oil obtained from fresh livers of *Gadus morrhua* Linné and other species of the Family *Gadidæ,* containing not more than 0.5 percent by volume of water and liver tissue. Nondestearinated Cod Liver Oil contains, in each g., not less than 255 mcg. (850 USP Units) of vitamin A and not less than 2.125 mcg. (85 USP Units) of vitamin D.

Description—Nondestearinated Cod Liver Oil is a thin, oily liquid at room temperature, having a characteristic, slightly fishy, but not a rancid, odor and a fishy taste. Nondestearinated Cod Liver Oil congeals or deposits stearin upon chilling.

Solubility—Nondestearinated Cod Liver Oil is slightly soluble in alcohol, and is freely soluble in ether and in chloroform.

Water and sediment, page 805—Nondestearinated Cod Liver Oil contains not more than 0.5 percent by volume of water and sediment.

Iodine value, page 804—The iodine value of Nondestearinated Cod Liver Oil is not less than 128 and not more than 180.

Identification for vitamin A, Color, Unsaponifiable matter, Acid value, and Saponification value—Nondestearinated Cod Liver Oil meets the requirements of the tests for *Identification for vitamin A, Color, Unsaponifiable matter, Acid value,* and *Saponification value* under *Cod Liver Oil,* page 182.

Assays—Proceed as directed in the *Assays* under *Cod Liver Oil,* page 182.

Packaging and storage—Preserve Nondestearinated Cod Liver Oil in tight containers. It may be stored in containers from which the air has been expelled by the production of a vacuum or by an inert gas.

Labeling—The vitamin A potency and vitamin D potency of Nondestearinated Cod Liver Oil, when designated on the label, are expressed in United States Pharmacopeia Units per g. of oil. These units may be referred to as USP Units.

CATEGORY—Pharmaceutic aid (source of cod liver oil).

Colistin Sulfate

Colistin Sulfate is the sulfate salt of an antibacterial substance produced by the growth of *Bacillus polymyxa* var. *colistinus.* It consists primarily of colistin A with small amounts of colistin B. It has a potency of not less than 500 mcg. of colistin base activity per mg. Colistin Sulfate conforms to the regulations of the federal

Food and Drug Administration concerning the certification of antibiotic drugs.

Description—Colistin Sulfate occurs as a white to slightly yellow, odorless, fine powder. A solution of Colistin Sulfate (1 in 100) has a pH between 4.0 and 7.0.

Solubility—Colistin Sulfate is freely soluble in water and slightly soluble in methanol. It is insoluble in acetone and in ether.

Packaging and storage—Preserve Colistin Sulfate in tight containers.

CATEGORY—Antibacterial (intestinal).

USUAL DOSE—**3** to **5 mg. per kg.** of body weight daily in three divided doses.

Colistin Sulfate for Oral Suspension

Colistin Sulfate for Oral Suspension is colistin sulfate admixed with one or more suitable suspending and dispersing agents, colors, flavors, buffers, and preservatives. It contains colistin sulfate equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of colistin base activity. Colistin Sulfate for Oral Suspension conforms to the regulations of the federal Food and Drug Administration concerning the certification of antibiotic drugs.

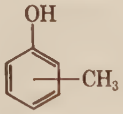
Packaging and storage—Preserve Colistin Sulfate for Oral Suspension in tight containers, protected from light.

Size available—Colistin Sulfate for Oral Suspension usually available contains an amount of colistin sulfate equivalent to 300 mg. colistin base activity in a 70-ml. container.

CATEGORY and DOSE—See Colistin Sulfate.

Colloidal Silicon Dioxide, page 633
Compound Amaranth Solution, page 36
Compound Benzaldehyde Elixir, page 75
Compound Cardamom Tincture, page 140
Compound Iodochlorhydroxyquin Powder, page 373
Compound Resorcinol Ointment, page 624
Compound Undecylenic Acid Ointment, page 751

Cresol



C_7H_8O Mol. wt. 108.14

Cresol is a mixture of isomeric cresols obtained from coal tar or from petroleum. It contains not more than 5.0 percent of C_6H_6O (phenol).

Description—Cresol is a colorless, or yellowish to brownish yellow, or pinkish, highly refractive liquid, becoming darker with age and on exposure to light. It has a phenol-like, sometimes empyreumatic odor. A saturated solution of Cresol is neutral or only slightly acid to litmus.

Solubility—Cresol is sparingly soluble in water, usually forming a cloudy solution. Cresol is miscible with alcohol, with ether, and with glycerin, and is dissolved by solutions of fixed alkali hydroxides.

Identification—To a saturated solution of Cresol add a few drops of ferric chloride T.S.: a bluish violet color is produced.

Specific gravity, page 866—The specific gravity of Cresol is not less than 1.030 and not more than 1.038.

Distilling range, *Method II*, page 782—Not less than 90 percent (v/v) of Cresol distils between 195° and 205°.

Hydrocarbons—A solution of 1 ml. of

Cresol in 60 ml. of water shows no more turbidity than that produced in 58 ml. of water by the addition of 1.5 ml. of 0.02 *N* sulfuric acid and 1 ml. of barium chloride T.S., comparison being made after the control mixture has been well shaken and allowed to stand for 5 minutes.

Phenol—

Dilute nitric acid—Blow air through nitric acid until the liquid is colorless, then mix 1 volume with 4 volumes of water.

Standard phenol solution—Dissolve about 1 g. of USP Phenol in about 100 ml. of water, and determine the actual C_6H_6O concentration as follows: Pipet 4.0 ml. of the solution into an iodine flask, add 30.0 ml. of 0.1 *N* bromine, then 5 ml. of hydrochloric acid, and immediately insert the stopper. Shake the flask repeatedly during 30 minutes, allow it to stand for 15 minutes, add quickly 5 ml. of potassium iodide solution (1 in 5), taking precautions against the escape of bromine vapor, and at once stopper the flask. Shake thoroughly, remove the stopper, and rinse it and the neck of the flask with a little water, so that the washings flow into the flask. Add 1 ml. of chloroform, shake the mixture well, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, adding starch T.S. as the end-point is neared. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 0.1 *N* bromine is equivalent to 1.569 mg. of C_6H_6O. Dilute a suitable volume of the solution with water so that each ml. contains 250 mcg. of C_6H_6O.

Procedure—Place about 2.5 g. of Cresol, accurately weighed, in a 250-ml. volumetric flask, add 10 ml. of sodium hydroxide solution (1 in 10), dilute with water to volume, and mix. Pipet 5.0 ml. of this solution into a 200-ml. volumetric flask, add 45 ml. of water and 1 drop of methyl orange T.S., neutralize with *Dilute nitric acid,* added dropwise, then dilute with water to volume, and mix. Pipet 5.0 ml. of the neutralized solution into each of two test tubes, 20 × 180 mm., graduated at the 25-ml. mark, and pipet 5.0 ml. of *Standard phenol solution* into each of two similar test tubes. To the contents of each tube add 5 ml. of Millon's reagent, allowing it to flow down the inner wall of the tube, mix, place the tubes simultaneously in a boiling water bath provided with a rack so that the tubes do not touch the bottom of the bath, and maintain the bath at boiling temperature for exactly 30 minutes. At once remove the tubes from the bath, cool them immediately and thoroughly by placing them in a bath of cold water for at least 10 minutes, add 5 ml. of *Dilute nitric acid* to each tube, and mix.

Add 3 ml. of dilute formaldehyde T.S. (formaldehyde T.S. diluted 1 in 50) to one of each pair of tubes, add water to all tubes to a volume of 25.0 ml., shake thoroughly, and allow to stand for 16 hours, during which time the added formaldehyde will impart a yellow color while the contents of the other 2 tubes acquire an orange-red color.

Pipet 20.0 ml. from each of the two tubes containing the *Standard phenol solution* into 100-ml. volumetric flasks, add 5 ml. of nitric acid, then add water to volume, and mix. Transfer the solutions to burets marked *B1* and *B2*, representing, respectively, the solution not treated and the solution treated with formaldehyde.

Pipet 10.0 ml. of the contents of the tube of formaldehyde-treated Cresol into a 50-ml. color-comparison tube marked *N1* and similarly add 10.0 ml. of the contents not treated with formaldehyde to a similar tube marked *N2*.

Add to tube *N1* the orange-red colored solution from buret *B1*, and add to tube *N2* an equal volume of the yellow-colored solution from buret *B2*, until the colors in tubes *N1* and *N2* match when observed in a colorimeter. Calculate the percentage of phenol by the formula $5V/W$, in which V is the volume, in ml., of *Standard phenol solution* taken from buret *B1*, and W is the weight, in g., of Cresol taken.

Packaging and storage—Preserve Cresol in tight, light-resistant containers.

CATEGORY—Disinfectant.

APPLICATION—1 to 5 percent solution on dishes, utensils, and other inanimate objects.

Saponated Cresol Solution

Saponated Cresol Solution contains, in each 100 ml., not less than 46 ml. and not more than 52 ml. of cresol. It is prepared by the saponification of a mixture of cresol with vegetable oils, or the mixed fatty acids derived therefrom, excluding coconut and palm kernel oils. The vegetable oil may be corn, cottonseed, linseed, or soya bean, or similar oils which have a saponification value, page 805, not greater than 205, and an iodine value, page 804, not less than 100.

Saponated Cresol Solution may be prepared extemporaneously in the following manner:

Cresol	**500 ml.**
The Vegetable Oil	**350 ml.**
Alcohol	**55 ml.**
Potassium Hydroxide	**73 g.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Mix the vegetable oil and the alcohol. Dissolve the potassium hydroxide in 100 ml. of purified water and immediately add this hot solution to the oil while vigorously stirring the mixture with a mechanical stirrer. Continue the stirring until a small portion of the soap dissolves in hot purified water to form a clear solution. Add the cresol to the soap, stir until a clear solution is obtained, and add sufficient purified water to make the Solution measure 1000 ml.

Note: If desired, 58 g. of the potassium hydroxide may be replaced by 37 g. of sodium hydroxide. It is also permissible to replace the alcohol with 20 ml. of oleic acid, in which case the oil should be warmed to 85° before the addition of the solution of the alkali hydroxide, and the mixture heated, if necessary, to complete saponification.

The quantities of potassium hydroxide and sodium hydroxide here directed have been determined upon the basis of the official minimum percentages of strength, namely, 85 percent and 95 percent, respectively. If either or both of the hydroxides used should have a different percentage of strength, corresponding alterations in the quantities should be made.

Characteristics of the liberated fatty acids—Place 50 ml. of Saponated Cresol Solution in a 1000-ml. round-bottom flask, and add 100 ml. of water and 30 ml. of diluted sulfuric acid. Connect the flask with a source of steam and a condenser and distil briskly with steam until 3 ml. of distillate produces not more than a faint opalescence upon the addition of 1 ml. of bromine T.S. Transfer the residual liquid to a separator, cool to room temperature, add 50 ml. of ether, shake well, and allow the layers to separate. Draw off the water layer as completely as possible and wash the ether layer three times with 50-ml. portions of cold water, rejecting the washings. Transfer the ether layer to a small flask containing 15 g. of anhydrous sodium sulfate, shake well, and decant the ether solution through a dry filter into a dry beaker. Carefully evaporate the ether and dry the mixed fatty acids at 105° for 1 hour. The acid value of the fatty acids is not more than 205, using about 1 g. of the fatty acids, accurately weighed, page 804, and the iodine value of the fatty acids is not less than 95, using from 150 to 250 mg. of the fatty acids, accurately weighed, page 804.

Assay—Mix in a 500-ml. distilling flask 50 ml. of Saponated Cresol Solution, accurately measured at 25°, with 150 ml. of kerosene. Add 3 g. of sodium bicarbonate, and distil the mixture, using an upright condenser, at the rate of not more than 2 drops per second, until the distillate comes over strongly yellow, receiving the distillate in a 250- to 300-ml. separator. Draw off the lower water layer, shake the kerosene layer with 10 ml. of sulfuric acid (49 to 51 percent, w/w), allow to stand for 2 hours, then draw off the acid layer completely, and discard it. Add to the kerosene layer 40 ml. of a 15 percent solution of sodium hydroxide, accurately measured at 25°, shake well for 5 minutes, allow to stand until complete separation has taken place, and draw off the sodium hydroxide layer into a graduated cylinder. Shake the kerosene layer again with a fresh portion of 20 ml. of the 15 percent sodium hydroxide solution, accurately measured at 25°, allow the two layers to separate completely, and draw off the sodium hydroxide layer into the graduated cylinder. Adjust the sodium hydroxide solution in the graduated cylinder to a temperature of 25°, and note its volume. The difference between the volume noted and the total volume of sodium hydroxide solution used represents the volume of cresol present in 50 ml. of Saponated Cresol Solution. This difference is not less than 23 ml. and not more than 26 ml.

Transfer the sodium hydroxide solution of the cresol obtained in the assay to a separator, and add sufficient hydrochloric acid to render the solution distinctly acid. Allow the liberated cresol to separate completely, and draw off the lower water layer. Wash the cresol with several successive portions of 20 ml. each of a saturated solution of calcium chloride until the washings are neutral or only slightly acid. Then add to the washed cresol about 5 g. of coarsely granular (about No. 4 mesh) anhydrous calcium chloride, shake gently at frequent intervals during 3 hours, and allow to stand overnight. Decant the clear liquid completely into a graduated 25-ml. cylinder and note its volume. Transfer the dehydrated cresol to a 50- to 60-ml. distilling flask, and distil as directed in *Method II* under *Boiling or Distilling Range or Temperature*, page 782, at the rate of about 1.5 ml. per minute, receiving the distillate in the cylinder in which the cresol was measured. At least 90 percent of the volume of cresol taken distils between 195° and 205°.

Alcohol content, page 772—Saponated Cresol Solution contains not more than 5 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Saponated Cresol Solution in tight containers.

CATEGORY—Disinfectant.

Cupric Sulfate

$CuSO_4.5H_2O$ Mol. wt. 249.68

Cupric Sulfate, dried at 250° to constant weight, contains not less than 98.5 percent and not more than 100.5 percent of $CuSO_4$.

Description—Cupric Sulfate occurs as deep blue, triclinic crystals, or as blue, crystalline granules or powder. It has a nauseous, metallic taste, and it effloresces slowly in dry air. Its solutions are acid to litmus.

Solubility—Cupric Sulfate is freely soluble in water and in glycerin. It is very soluble in boiling water and slightly soluble in alcohol.

Identification—A solution of Cupric Sulfate (1 in 10) responds to the tests for *Copper*, page 808, and for *Sulfate*, page 810.

Loss on drying, page 814—Dry Cupric Sulfate at 250° to constant weight: it loses not less than 33 percent and not more than 36.5 percent of its weight.

Alkalies and alkaline earths—Dissolve 2 g. of Cupric Sulfate in 100 ml. of water, add 1 ml. of diluted hydrochloric acid, and pass hydrogen sulfide through the solution until all of the copper is precipitated. Filter the mixture, evaporate 50 ml. of the filtrate to dryness, and ignite: the weight of the residue does not exceed 3 mg. (0.3 percent).

Assay—Weigh accurately about 650 mg. of Cupric Sulfate, previously dried at 250° to constant weight, dissolve it in 50 ml. of water, add 4 ml. of acetic acid and 3 g. of potassium iodide, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 15.96 mg. of $CuSO_4$.

Packaging and storage—Preserve Cupric Sulfate in tight containers.

CATEGORY—Antidote (phosphorus).

Cyanocobalamin Co 60 Capsules

Cyanocobalamin Co 60 Capsules contain cyanocobalamin in which a portion of the molecules contain radioactive cobalt (^{60}Co) in the molecular structure. Cyanocobalamin Co 60 Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{60}Co as cyanocobalamin expressed in microcuries at the time indicated in the labeling. The activity of each capsule in not less than 97.0 percent and not more than 103.0 percent of the mean radioactivity of the individual capsules of the lot. The cyanocobalamin content is not less than 90.0 percent and not more than 110.0 percent of the labeled amount. The specific activity is not less than 0.5 microcurie per mcg. of cyanocobalamin. Significant quantities of other radionuclides are absent.

Caution—In making dosage calculations, correct for radioactive decay. The radioactive half-life of ^{60}Co *is 5.27 years.*

Description—Cyanocobalamin Co 60 Capsules may contain a small, rectangular solid, or may appear empty.

Radionuclide identification—A solution of 1 or more Cyanocobalamin Co 60 Capsules in water responds to the test for *Radionuclide identification* under *Cyanocobalamin Co 60 Solution*, page 188.

Cyanocobalamin content—Determine the content, in mcg. per Capsule, of cyanocobalamin as directed under *Vitamin B_{12} Activity Assay*, page 892.

Content uniformity—Determine the radioactivity, in counts per minute, of each capsule by measurement in a suitable counting assembly and under identical geometrical conditions. Calculate the mean radioactivity of the individual capsules.

Assay for radioactivity—Determine the radioactivity, in counts per minute, of a calibrated cobalt 60 standard by measurement in a suitable counting assembly, adjusting the concentration of the standard so as to obtain optimum counting accuracy with the particular assembly used. Dissolve 1 or more Cyanocobalamin Co 60 Capsules in water, and adjust the concentration as for the standard. Transfer an accurately measured aliquot to a container identical to that used for the standard, and determine the radioactivity at approximately the same time and under the identical geometrical conditions used for the standard. Correct both determinations for background, and calculate the radioactivity, in microcuries per Capsule, by the formula $SD \times (A/B)$, in which S is the microcurie strength of the standard, D is the dilution factor, and A and B are the radioactivities expressed in counts per minute of the sample and the standard, respectively.

Packaging and storage—Preserve Cyanocobalamin Co 60 Capsules in well-closed containers.

Expiration date—The expiration date of Cyanocobalamin Co 60 Capsules is not later than 6 months after date of calibration.

Labeling—Label Cyanocobalamin Co 60 Capsules to include the following: the name of the Capsules; the name, address, and batch or lot number of the manufacturer; the time and date of calibration; the amount of cyanocobalamin expressed in mcg. per Capsule; the amount of ^{60}Co as cyanocobalamin expressed in microcuries per Capsule at the time and date of calibration; the warning, "Caution—Radioactive Material"; and the statement, "Do not use after 6 months from date of calibration."

Capsules available—Cyanocobalamin Co 60 Capsules are usually available in such sizes as may be requested by the physician.

CATEGORY—Diagnostic aid (pernicious anemia).

USUAL DOSE—**0.5** to **2 mcg.**, containing not more than 1 microcurie.

USUAL DOSE RANGE—The equivalent of 0.5 to 1 microcurie.

Cyanocobalamin Co 60 Solution

Cyanocobalamin Co 60 Solution is a solution suitable for oral administration, containing cyanocobalamin in which a portion of the molecules contain radioactive cobalt ^{60}Co in the molecular structure. Cyanocobalamin Co 60 Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{60}Co as cyanocobalamin expressed in microcuries at the time indicated in the labeling. The cyanocobalamin content is not less than 90.0 percent and not more than 110.0 percent of the labeled amount per ml. The amount of cobalt 60 as cyanocobalamin is not more than 1 microcurie per ml. The specific activity is not less than 0.5 microcurie per mcg. of cyanocobalamin. Significant quantities of other radionuclider are abcent. Cyanocobalamin Co 60 Solution contains a suitable bacteriostatic agent.

Caution—In making dosage calculations, correct for radioactive decay. The radioactive half-life of ^{60}Co is 5.27 years.

Description—Cyanocobalamin Co 60 Solution is a clear, colorless to pink solution.

Radionuclide identification—The gamma-ray scintillation spectrum of Cyanocobalamin Co 60 Solution is identical to that of a specimen of cobalt 60 of known purity, which exhibits photoelectric peaks having energies of 1.172 Mev. and 1.332 Mev.

pH, page 824—The pH of Cyanocobalamin Co 60 Solution is between 4.0 and 5.5.

Radiochemical purity—Place 0.01 ml. of a solution, containing 1 mg. of cyanocobalamin per ml., about 45 mm. from one end of a 25 × 300-mm. strip of chromatographic paper (see *Chromatography*, page 786), and allow to dry. To the same area add a measured volume, representing an activity of not less than 20,000 counts per minute, of appropriately diluted Cyanocobalamin Co 60 Solution, and allow to dry. Develop the chromatogram over a period of about 24 hours by descending chromatography, using a freshly prepared homogeneous solution prepared by mixing 1 liter of secondary butyl alcohol, 1 ml. of stronger ammonia water, 20 ml. of sodium cyanide solution (3.5 in 1000), and 300 ml. of water (if phases separate, add 10-ml. increments of secondary butyl alcohol and shake until the mixture becomes homogeneous). Remove the paper strip from the apparatus when the cyanocobalamin spot has moved at least 75 mm. from the point of application. Dry the chromatogram in air, and determine the radioactivity distribution by scanning with a suitable collimated radiation detector, or section the strip into sections not exceeding 65 mm. in width and determine the radioactivity of the individual sections. The radioactivity of the cyanocobalamin band is not less than 95 percent of the total radioactivity. (*Caution:* Cyanocobalamin solutions are sensitive to light. Perform the preparation of strips in diffuse light and the development and drying of strips in the absence of light.)

Cyanocobalamin content—Determine the content, in mcg. per ml., of cyanocobalamin as directed under *Vitamin B_{12} Activity Assay*, page 892.

Assay for radioactivity—Determine the radioactivity, in counts per minute, of a calibrated cobalt 60 standard by measurement in a suitable counting assembly, adjusting the concentration of the standard so as to obtain optimum counting accuracy with the particular assembly used. Transfer an accurately measured aliquot of Cyanocobalamin Co 60 Solution, appropriately diluted, to a container identical to that used for the standard, and determine the radioactivity at approximately the same time and under the identical geometrical conditions used for the standard. Correct both determinations for background, and calculate the radioactivity, in microcuries per ml., by the formula $SD \times (A/B)$, in which S is the microcurie strength of the standard, D is the dilution factor, and A and B are the radioactivities expressed in counts per minute of the sample and the standard, respectively.

Packaging and storage—Preserve Cyanocobalamin Co 60 Solution in single-dose or in multiple-dose containers.

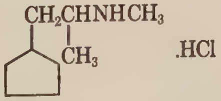
Expiration date—The expiration date of Cyanocobalamin Co 60 Solution is not later than 6 months after date of calibration.

Labeling—Label Cyanocobalamin Co 60 Solution to include the following: the name of the Solution; the name, address, and batch or lot number of the manufacturer; the time and date of calibration; the amount of ^{60}Co as cyanocobalamin expressed as total microcuries and as microcuries per ml. at the time and date of calibration; the amount of cyanocobalamin expressed in mcg. per ml.; the name and quantity of the added preservative; the warning, "Caution—Radioactive Material"; and the statement, "Do not use after 6 months from date of calibration."

CATEGORY and DOSE—See Cyanocobalamin Co 60 Capsules.

Cyclamate, Calcium, page 118
Cyclamate, Calcium, and Calcium Saccharin Solution, page 120
Cyclamate, Calcium, and Calcium Saccharin Tablets, page 121
Cyclamate, Sodium, page 642
Cyclamate, Sodium, and Sodium Saccharin Solution, page 644
Cyclamate, Sodium, and Sodium Saccharin Tablets, page 644

Cyclopentamine Hydrochloride



N,α-Dimethylcyclopentaneethylamine Hydrochloride

$C_9H_{19}N.HCl$ Mol. wt. 177.72

Cyclopentamine Hydrochloride, dried at 80° for 3 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_9H_{19}N.HCl$.

Description—Cyclopentamine Hydrochloride occurs as a white, crystalline powder, possessing a mild characteristic odor and a bitter taste. The pH of a 1 in 100 solution is about 6.

Solubility—Cyclopentamine Hydrochloride is freely soluble in water and in alcohol. It is sparingly soluble in benzene and is freely soluble in chloroform. It is slightly soluble in ether.

Identification—

A: To 2 ml. of a solution of Cyclopentamine Hydrochloride (1 in 40), add 500 mg. of sodium nitrite and boil gently for about 30 seconds. (A turbidity may develop.) Cool, and add 1.5 ml. of hydrochloric acid dropwise, with additional cooling, if necessary: a yellowish orange, oily material separates. Add more hydrochloric acid dropwise, with agitation, until the oily layer disappears and a white precipitate forms. Decant the supernatant liquid, and add about 5 ml. of water: the precipitate dissolves (*presence of secondary amine*).

B: A solution of Cyclopentamine Hydrochloride (1 in 20) responds to the tests for *Chloride*, page 808.

Melting range, page 814—Cyclopentamine Hydrochloride melts, within a 2° range, between 111° and 117°.

Loss on drying, page 814—Dry Cyclopentamine Hydrochloride at 80° for 3 hours: it loses not more than 0.4 percent of its weight.

Residue on ignition, page 858—Cyclopentamine Hydrochloride yields not more than 0.05 percent of residue on ignition.

Assay—Dissolve about 350 mg. of Cyclopentamine Hydrochloride, previously dried at 80° for 3 hours and accurately weighed, in 50 ml. of glacial acetic acid, and add 1 drop of crystal violet T.S. and 10 ml. of mercuric acetate T.S. Titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 17.77 mg. of $C_9H_{19}N.HCl$.

Packaging and storage—Preserve Cyclopentamine Hydrochloride in tight containers.

CATEGORY—Adrenergic (vasoconstrictor).

USUAL DOSE—Intramuscular, **25 mg.** Intravenous, **5** to **10 mg.** Intranasal, 1 or 2 drops of a 0.5 or 1 percent solution every 3 or 4 hours.

Cyclopentamine Hydrochloride Injection

Cyclopentamine Hydrochloride Injection is a sterile solution of cyclopentamine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_9H_{19}N.HCl$.

Identification—Cyclopentamine Hydrochloride Injection responds to the *Identification tests* under *Cyclopentamine Hydrochloride Solution*, page 190.

Other requirements—Cyclopentamine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—Transfer an accurately measured volume of Cyclopentamine Hydrochloride Injection, equivalent to about 125 mg. of cyclopentamine hydrochloride, to a separator and add water to bring the volume to about 15 ml. Saturate the solution with sodium chloride and add 5 ml. of sodium hydroxide T.S. Extract with 25 ml. of ether, followed by five additional extractions, using 10-ml. portions of ether. Collect the ether extracts in a 250-ml. separator, and wash with 5-ml. portions of water until the water is neutral to litmus. Collect the water washings in a separator and extract with 10 ml. of ether, and then combine with the other ether extracts. Extract with 20.0 ml. of 0.05 *N* sulfuric acid, followed by two 10-ml. portions of water. Combine the extracts in a beaker, and warm on a steam bath to remove the ether. Cool, add 3 drops of methyl red T.S., and titrate with 0.02 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction (see *Residual Titrations*, page 883). Each ml. of 0.02 *N* sulfuric acid is equivalent to 3.554 mg. of $C_9H_{19}N.HCl$.

Packaging and storage—Preserve Cyclopentamine Hydrochloride Injection in single-dose containers, preferably of Type I glass.

Injection available—Cyclopentamine Hydrochloride Injection usually available contains the following amount of cyclopentamine hydrochloride: 25 mg. in 1 ml.

CATEGORY and DOSE—See Cyclopentamine Hydrochloride.

Cyclopentamine Hydrochloride Solution

Cyclopentamine Hydrochloride Solution is cyclopentamine hydrochloride in a suitable isotonic vehicle. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_9H_{19}N.HCl$.

Identification—Transfer to a 125-ml. separator a volume of Cyclopentamine Hydrochloride Solution, equivalent to about 50 mg. of cyclopentamine hydrochloride, add 5 ml. of sodium hydroxide T.S., extract the liberated base with 20 ml. of ether, and evaporate the ether on a steam bath. Dissolve the residue in 2 ml. of water, add 5 drops of diluted hydrochloric acid and about 500 mg. of sodium nitrite, and boil gently for about 30 seconds. (A turbidity may develop.) Proceed as directed in *Identification test A* under *Cyclopentamine Hydrochloride*, page 189, beginning with "Cool, and add 1.5 ml. of hydrochloric acid dropwise. . . ."

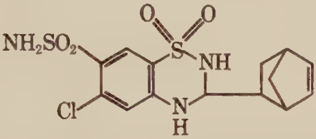
Assay—Proceed with Cyclopentamine Hydrochloride Solution as directed in the *Assay* under *Cyclopentamine Hydrochloride Injection*, page 190.

Packaging and storage—Preserve Cyclopentamine Hydrochloride Solution in tight containers.

Solutions available—Cyclopentamine Hydrochloride Solution usually available contains 0.5 and 1 percent of cyclopentamine hydrochloride.

Category and Dose—See Cyclopentamine Hydrochloride.

Cyclothiazide



6-Chloro-3,4-dihydro-3-(5-norbornen-2-yl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide

$C_{14}H_{16}ClN_3O_4S_2$ Mol. wt. 389.88

Cyclothiazide contains not less than 97.0 percent and not more than 101.5 percent of $C_{14}H_{16}ClN_3O_4S_2$, calculated on the anhydrous basis.

Description—Cyclothiazide occurs as a white to nearly white, practically odorless powder.

Solubility—Cyclothiazide is practically insoluble in water and in chloroform, sparingly soluble in alcohol, and freely soluble in acetone and in methanol.

Identification—Transfer 20 mg. of Cyclothiazide to a test tube, and dissolve in 5 ml. of methanol. Add 1 ml. of hydrochloric acid and warm on a steam bath for 5 minutes: the liquid acquires a blue color and a yellow fluorescence.

Melting range, page 814—Cyclothiazide melts within a range of 4° between 217° and 225°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Cyclothiazide, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Cyclothiazide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Cyclothiazide in methanol exhibits maxima and minima at the same wavelengths as that of NF Cyclothiazide Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance occurring at about 271 mμ, do not differ by more than 3 percent.

Water, page 900—Determine the water content of Cyclothiazide by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Cyclothiazide yields not more than 0.2 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 200 mg. of Cyclothiazide meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Assay—Dissolve about 400 mg. of Cyclothiazide, accurately weighed, in 40 ml. of ethylenediamine, add 5 drops of a solution of *o*-nitroaniline in benzene (1 in 100), and titrate with 0.1 *N* sodium methoxide using a magnetic stirrer. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium methoxide is equivalent to 19.49 mg. of $C_{14}H_{16}ClN_3O_4S_2$.

Packaging and storage—Preserve Cyclothiazide in well-closed containers.

Category—Diuretic; antihypertensive.

Usual dose range—Diuretic—Initial, **1 to 2 mg.** daily; maintenance, **1 to 2 mg.** every other day or two or three times a week. Antihypertensive, **2 mg.** one to three times a day.

Cyclothiazide Tablets

Cyclothiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_{16}ClN_3O_4S_2$.

Identification—The solution prepared from Cyclothiazide Tablets as directed in the *Assay* exhibits ultraviolet absorption maxima and minima at the same wavelengths as that of NF Cyclothiazide Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Cyclothiazide Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Cyclothiazide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 200-ml. volumetric flask, add 100 ml. of methanol, and shake mechanically for 30 minutes. Dilute to volume with methanol, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol to provide a solution containing approximately 10 mcg. of cyclothiazide per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Cyclothiazide Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 271 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{14}H_{16}ClN_3O_4S_2$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of cyclothiazide in the tablet; D is the exact concentration, in mcg. per ml., of cyclothiazide in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

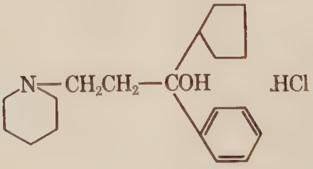
Assay—Weigh and finely powder not less than 20 Cyclothiazide Tablets. Weigh accurately a portion of the powder, equivalent to about 2 mg. of cyclothiazide, and transfer to a separator. Add 5 ml. of water and extract with four 25-ml. portions of a mixture of chloroform and methanol (4:1), filtering each portion through chloroform-washed cotton into a suitable beaker. Evaporate the combined extracts to dryness on a steam bath in a current of air. Transfer the residue quantitatively with the aid of about 100 ml. of methanol to a 200-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Cyclothiazide Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 271 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{14}H_{16}ClN_3O_4S_2$ in the portion of Tablets taken by the formula $0.2C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Cyclothiazide Tablets in well-closed containers.

Tablets available—Cyclothiazide Tablets usually available contain the following amount of cyclothiazide: 2 mg.

CATEGORY and DOSE—See Cyclothiazide.

Cycrimine Hydrochloride*



α-Cyclopentyl-α-phenyl-1-piperidinepropanol Hydrochloride

$C_{19}H_{29}NO.HCl$ Mol. wt. 323.91

Cycrimine Hydrochloride, dried at 105° for 5 hours, contains not less than 97.0 percent and not more than 100.5 percent of $C_{19}H_{29}NO.HCl$.

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* Patented. See notice, page ii.

Description—Cycrimine Hydrochloride occurs as a white, odorless solid, possessing a bitter taste.

Solubility—Cycrimine Hydrochloride is slightly soluble in water, and is sparingly soluble in chloroform and in alcohol.

Identification—

A: To 5 ml. of a solution of Cycrimine Hydrochloride (1 in 200) add 2 drops of nitric acid: the solution responds to the test for *Chloride,* page 808, using 1 ml. of silver nitrate T.S.

B: To 40 ml. of a solution of Cycrimine Hydrochloride (1 in 200) add 5 ml. of sodium hydroxide T.S., cool the mixture overnight, filter, wash the precipitate with cold water, and dry in vacuum over phosphorus pentoxide for 5 hours: the cycrimine so obtained melts between 90° and 96°, page 814.

Melting range, *Class Ia,* page 815—Cycrimine Hydrochloride melts with decomposition between 241° and 244°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Cycrimine Hydrochloride, previously dried at 105° for 5 hours, exhibits maxima only at the same wavelengths as that of NF Cycrimine Hydrochloride Reference Standard, similarly measured.

pH, page 824—The pH of a solution of Cycrimine Hydrochloride (1 in 200) is between 5.2 and 5.8.

Loss on drying, page 814—Dry Cycrimine Hydrochloride at 105° for 5 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Cycrimine Hydrochloride yields not more than 0.1 percent of residue on ignition. Retain the residue from a 1-g. sample for the *Heavy metals test.*

Heavy metals, page 806—Dissolve the residue resulting from the *Residue on ignition test* in 23 ml. of water and add 2 ml. of diluted acetic acid: the heavy metals limit for Cycrimine Hydrochloride is 20 parts per million.

Assay—Transfer to a 250-ml. conical flask about 600 mg. of Cycrimine Hydrochloride, previously dried at 105° for 5 hours and accurately weighed, dissolve it in 50 ml. of glacial acetic acid, using heat if necessary, and add 10 ml. of mercuric acetate T.S. Cool the solution to room temperature, add 1 drop of crystal violet T.S., and titrate with 0.1 N perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N perchloric acid is equivalent to 32.39 mg. of $C_{19}H_{29}NO.HCl$.

Packaging and storage—Preserve Cycrimine Hydrochloride in tight containers.

CATEGORY—Anticholinergic.

USUAL DOSE—Initial, **1.25 mg.** three times a day. Maintenance, to be determined by the physician.

USUAL DOSE RANGE—**1.25 to 5 mg.**

Cycrimine Hydrochloride Tablets

Cycrimine Hydrochloride Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $C_{19}H_{29}NO.HCl$.

Identification—Triturate a portion of powdered Cycrimine Hydrochloride Tablets, equivalent to about 300 mg. of cycrimine hydrochloride, with three 25-ml. portions of chloroform, filter through a pledget of cotton, and evaporate the filtrate to dryness on a steam bath. The residue responds to the *Identification tests* under *Cycrimine Hydrochloride,* page 192.

Disintegration, page 878—The disintegration time limit for Cycrimine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Cycrimine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Bromocresol purple solution—Dissolve 250 mg. of bromocresol purple in sufficient dilute acetic acid (1 in 50) to make 1000 ml.

Standard preparation—Transfer about 25 mg. of NF Cycrimine Hydrochloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with *Bromocresol purple solution,* and mix.

Assay preparation—Weigh and finely powder not less than 20 Cycrimine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 2.5 mg. of cycrimine hydrochloride, to a 100-ml. volumetric flask, add 10.0 ml. of water, and mix well. Dilute to volume with *Bromocresol purple solution,* mix thoroughly, and allow the undissolved particles to settle. Use the supernatant liquid as directed in the *Procedure.*

Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 60-ml. separators. Transfer 0.5 ml. of water and 4.5 ml. of *Bromocresol purple solution* to a third separator to serve as the blank. Extract each solution with 20 ml. of chloroform, and filter each extract, discarding the first

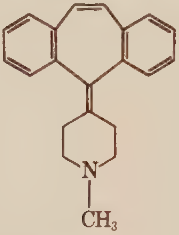
5 ml. of filtrate. Concomitantly determine the absorbance of each subsequent filtrate in 1-cm. cells, at the maximum at about 405 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{19}H_{29}NO.HCl$ in the portion of Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Cycrimine Hydrochloride Tablets in tight containers.

Tablets available—Cycrimine Hydrochloride Tablets usually available contain the following amounts of cycrimine hydrochloride: 1.25 and 2.5 mg.

CATEGORY and DOSE—See Cycrimine Hydrochloride.

Cyproheptadine Hydrochloride*



$.HCl.1^1/_2H_2O$

4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine Hydrochloride

$C_{21}H_{21}N.HCl.1^1/_2H_2O$ Mol. wt. (anhydrous) 323.87

Cyproheptadine Hydrochloride, dried in vacuum at 100° to constant weight, contains not less than 98.5 percent and not more than 100.5 percent of $C_{21}H_{21}N.HCl$.

Description—Cyproheptadine Hydrochloride occurs as a white to slightly yellow, odorless or practically odorless, crystalline powder.

Solubility—Cyproheptadine Hydrochloride is slightly soluble in water, sparingly soluble in alcohol, and freely soluble in methanol. It is soluble in chloroform and practically insoluble in ether.

Identification—Dissolve 100 mg. of Cyproheptadine Hydrochloride in 10 ml. of methanol. Place 1 drop of the solution on a filter paper, dry, and view under shortwave ultraviolet light: a bright blue fluorescence is observed.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Cyproheptadine Hydrochloride exhibits maxima only at the same wavelengths as that of NF Cyproheptadine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 62,500 solution of Cyproheptadine Hydrochloride in alcohol exhibits maxima and minima at the same wavelengths as that of NF Cyproheptadine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 286 mμ, do not differ by more than 3 percent.

Acidity—Dissolve 1 g. of Cyproheptadine Hydrochloride in 25 ml. of methanol, add 3 drops of methyl red T.S., and titrate with 0.1 *N* sodium hydroxide: not more than 0.15 ml. is required (0.05 percent as HCl).

Loss on drying, page 814—Dry Cyproheptadine Hydrochloride in vacuum at 100° to constant weight, maintaining the pressure between 1 mm. and 5 mm. of mercury: it loses not less than 7 percent and not more than 9 percent of its weight.

Residue on ignition, page 858—Cyproheptadine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Cyproheptadine Hydrochloride is 30 parts per million.

Assay—Dissolve about 650 mg. of Cyproheptadine Hydrochloride, previously dried in vacuum at 100° to constant weight and accurately weighed, in 50 ml. of glacial acetic acid, heating to effect solution. Cool, add 10 ml. of mercuric acetate T.S., 0.5 ml. of acetic anhydride, and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 32.39 mg. of $C_{21}H_{21}N.HCl$.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Cyproheptadine Hydrochloride in well-closed containers.

CATEGORY—Antihistaminic; antipruritic.

USUAL DOSE—4 mg. three or four times a day.

USUAL DOSE RANGE—4 to 20 mg. a day.

Cyproheptadine Hydrochloride Syrup

Cyproheptadine Hydrochloride Syrup contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{21}N.HCl$.

Identification—Transfer a volume of Cyproheptadine Hydrochloride Syrup, equivalent to about 20 mg. of cyproheptadine hydrochloride, into a 125-ml. separator, add 20 ml. of sodium bicarbonate solution (1 in 25), and extract with 50 ml. of isooctane. Wash the isooctane extracts with 15 ml. of the sodium bicarbonate solution, and discard the aqueous phase. Filter the isooctane into a 125-ml. conical flask, and evaporate to a few ml. on a steam bath with the aid of a current of air. Complete the evaporation to dryness with the air current at room temperature. Dissolve the residue in 2 ml. of methanol, transfer 3 drops to a filter paper, allow to dry, and view under shortwave ultraviolet light: a bright blue fluorescence is observed.

Reaction—Cyproheptadine Hydrochloride Syrup is acid to litmus.

Assay—Transfer to a 125-ml. separator an accurately measured volume of Cyproheptadine Hydrochloride Syrup, equivalent to about 2 mg. of anhydrous cyproheptadine hydrochloride, add 20 ml. of sodium bicarbonate solution (1 in 100), and extract with two 25-ml. portions of isooctane. Wash the combined isooctane extracts with 15 ml. of the sodium bicarbonate solution, and discard the washing. Extract the isooctane solution with one 50-ml. portion and one 25-ml. portion of 0.1 *N* hydrochloric acid, collecting the aqueous acid extract in a 100-ml. volumetric flask. Dilute to volume with 0.1 *N* hydrochloric acid, and mix. Filter a portion of the solution through dry filter paper, discarding the first 20 ml. of filtrate. Concomitantly determine the absorbance of the subsequent filtrate and of a solution of NF Cyproheptadine Hydrochloride Reference Standard, in 0.1 *N* hydrochloric acid at a concentration of about 20 mcg. of anhydrous cyproheptadine hydrochloride per ml., in 1-cm. cells, with a suitable spectrophotometer, at the maximum at about 286 mμ, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{21}H_{21}N.HCl$ in each ml. of the Syrup taken by the formula $0.1 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, calculated on the anhydrous basis, of the Reference Standard solution, in mcg. per ml., V is the volume, in ml., of the Syrup taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Cyproheptadine Hydrochloride Syrup in tight containers.

Syrup available—Cyproheptadine Hydrochloride Syrup usually available contains the following amount of anhydrous cyproheptadine hydrochloride: 2 mg. in 5 ml.

CATEGORY and DOSE—See Cyproheptadine Hydrochloride.

Cyproheptadine Hydrochloride Tablets

Cyproheptadine Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{21}N.HCl$.

Identification—Powder a Cyproheptadine Hydrochloride Tablet, transfer to a suitable flask, add 1 ml. of methanol, stopper, and shake for 10 minutes. Filter, transfer a few drops of filtrate to a new filter paper, dry, and view under shortwave ultraviolet light: a bright blue fluorescence is observed.

Disintegration, page 878—The disintegration time limit for Cyproheptadine Hydrochloride Tablets is 15 minutes.

Content uniformity, *Method I*, page 799—Cyproheptadine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Mixed solvent—Prepare a solution by mixing 10 ml. of methanol, 2 drops of hydrochloric acid, and sufficient water-saturated chloroform to make 100 ml.

Standard preparation—Dissolve a suitable quantity of NF Cyproheptadine Hydrochloride Reference Standard, accurately weighed, in the *Mixed solvent*, and prepare, by quantitative and stepwise dilution, a solution containing about 20 mcg. per ml.

Assay preparation—Weigh and finely powder not less than 20 Cyproheptadine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 4 mg. of cyproheptadine hydrochloride, to a 100-ml. beaker, add 1 ml. of spectrograde dimethyl sulfoxide (see page 915), and mix thoroughly to wet the powder evenly. Add 1 ml. of sulfamic acid solution (1 in 20), mix, add 3 g. of purified siliceous earth, and mix until a fluffy mixture is obtained.

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 250-mm. test tube to which is fused a 5-cm. length of 7-mm. tubing) with the aid of a tamping rod about 45 cm. long and having a disk with a diameter of about 1 mm. less than that of the tube. To 2 g. of purified siliceous earth in a 100-ml. beaker add 1 ml. of sulfamic acid solution (1 in 20), and mix until a fluffy mixture is obtained. Transfer the mixture to the column, and tamp gently to compress the material to a uniform mass. Transfer the *Assay preparation* to the column, scrub the beaker with a mixture of 1 g. of the siliceous earth and 3 drops of the sulfamic acid solution, transfer this to the column, tamp as above, and add a pledget of glass wool to the top of the column.

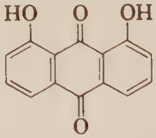
Procedure—Wash the column with 100 ml. of water-saturated ether, and discard the washings. Place under the column, as a receiver, a 200-ml. volumetric flask containing 20 ml. of methanol and 4 drops of hydrochloric acid. Pass through the column 150 ml. of water-saturated chloroform. Mix the eluate, allow to cool to room temperature, dilute to volume with water-saturated chloroform, and mix. Concomitantly determine the absorbance of this solution and of the *Standard preparation*, in 1-cm. cells at the maximum at about 286 mμ, with a suitable spectrophotometer, using the *Mixed solvent* as the blank. Record the absorbance of the *Standard preparation* as A_S, and record the absorbance of the solution from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{21}N.HCl$ in the portion of tablets taken by the formula $0.2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of anhydrous cyproheptadine hydrochloride in the *Standard preparation*.

Packaging and storage—Preserve Cyproheptadine Hydrochloride Tablets in well-closed containers.

Tablets available—Cyproheptadine Hydrochloride Tablets usually available contain the following amount of cyproheptadine hydrochloride: 4 mg.

Category and Dose—See Cyproheptadine Hydrochloride.

Danthron



1,8-Dihydroxyanthraquinone

$C_{14}H_8O_4$ Mol. wt. 240.22

Danthron contains not less than 95.0 percent and not more than 105.0 percent of $C_{14}H_8O_4$.

Description—Danthron occurs as an orange-colored, crystalline powder.

Solubility—Danthron is practically insoluble in water. It is soluble in alcohol, in ether, in benzene, in chloroform, and in solutions of sodium hydroxide.

Identification—

A: Dissolve about 100 mg. of Danthron in 1 ml. of sulfuric acid: a red solution is produced. Dilute the solution with water: a yellow precipitate is formed.

B: Dissolve about 50 mg. of Danthron in 10 ml. of ether, add 5 ml. of ammonia T.S., and shake thoroughly: the water layer is red in color.

Melting range, page 814—Danthron begins to sublime at about 75°, and melts between 190° and 195°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Danthron, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Danthron Reference Standard, similarly measured.

Ultraviolet absorption, page 866—A 1 in 50,000 solution of Danthron in benzene exhibits maxima and minima at the same wavelengths as that of NF Danthron Reference Standard, similarly measured.

Heavy metals, page 806—To 2 g. of Danthron add 5 ml. of diluted acetic acid and sufficient water to make 50 ml., shake the mixture for about 5 minutes, and filter. Extract the filtrate with four 25-ml. portions of ethylene dichloride to remove the yellow coloring material, and determine the heavy metals content on a 25-ml. portion of the filtrate: the heavy metals limit for Danthron is 50 parts per million.

Mercury—Danthron contains not more than 50 parts per million of mercury when tested according to the *Mercury Limit Test,* page 816.

Assay—Transfer to a 100-ml. volumetric flask about 200 mg. of Danthron, accurately weighed, add benzene to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with benzene, and mix. Transfer 10.0 ml. of this solution to a third 100-ml. volumetric flask, dilute to volume with benzene, and mix. Concomitantly determine the absorbance of this solution, and of a solution of NF Danthron Reference Standard, in benzene, at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 432 mμ, with a suitable spectrophotometer, using benzene as the blank. Calculate the quantity, in mg. of $C_{14}H_8O_4$ in the Danthron taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Danthron in well-closed containers.

Category—Cathartic.
Usual dose—**75 to 150 mg.**

Danthron Tablets

Danthron tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_8O_4$.

Identification—

A: Finely powder a number of Danthron Tablets, equivalent to about 150 mg. of danthron, and transfer to a glass-stoppered centrifuge tube. Add 25 ml. of ether, shake, and allow to stand, with frequent shaking, for 15 minutes. Transfer 15 ml. of the clear supernatant liquid to a small beaker, and evaporate to dryness under a stream of air. Add 1 ml. of sulfuric acid, and swirl to dissolve the residue: a red solution is produced. Dilute the solution with water: a yellow precipitate is formed.

B: Transfer 5 ml. of the clear supernatant liquid obtained in *Identification test A* to a small glass-stoppered tube, add 3 ml. of ammonia T.S., and shake vigorously: the water layer becomes red in color.

Disintegration, page 878—The disintegration time limit for Danthron Tablets is 30 minutes.

Weight variation, page 901—Danthron Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Danthron Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of danthron, to a 50-ml. volumetric flask, add about 40 ml. of chloroform, and allow to stand for about 15 minutes with frequent swirling to aid dissolution. Dilute to volume with chloroform, and mix. Transfer a portion of the mixture to a glass-stoppered centrifuge tube, and centrifuge until the solids are separated. Transfer 1.0 ml. of the clear supernatant liquid to a 50-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Danthron Reference Standard, in the same medium, at a concentration of about 8 mcg. per ml., in 1-cm. cells, at the maximum at about 430 mμ, with a suitable spectrophotometer, using a mixture of chloroform and alcohol (1 in 50) as the blank. Calculate the quantity, in mg., of $C_{14}H_8O_4$ in the portion of the Tablets taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

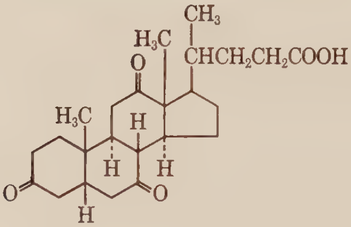
Packaging and storage—Preserve Danthron Tablets in well-closed containers.

Tablets available—Danthron Tablets usually available contain the following amount of danthron: 75 mg.

Category and Dose—See Danthron.

Dehydrocholate, Sodium, Injection, page 645

Dehydrocholic Acid



3,7,12-Trioxo-5β-cholan-24-oic Acid

$C_{24}H_{34}O_5$ Mol. wt. 402.54

Dehydrocholic Acid contains not less than 98.5 percent and not more than 101.0 percent of $C_{24}H_{34}O_5$, calculated on the dried basis. Dehydrocholic Acid for parenteral use melts between 237° and 242°.

Description—Dehydrocholic Acid occurs as a white, fluffy, odorless powder, having a bitter taste.

Solubility—Dehydrocholic Acid is practically insoluble in water and is slightly soluble in ether. It is slightly soluble in alcohol and sparingly soluble in chloroform, the solutions in these solvents usually being slightly turbid. Dehydrocholic Acid is soluble in glacial acetic acid and in solutions of alkali hydroxides and carbonates.

Melting range, *Class Ia,* page 815—Dehydrocholic Acid melts within a range of 3° between 231° and 242°.

Specific rotation, page 822—The specific rotation of Dehydrocholic Acid, calculated on the dried basis, determined in a solution in dioxane containing 200 mg. of Dehydrocholic Acid in each 10 ml., is not less than +29° and not more than +32.5°.

Loss on drying, page 814—Dry Dehydrocholic Acid at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Dehydrocholic Acid yields not more than 0.3 percent of residue on ignition.

Odor on boiling—Boil 2 g. of Dehydrocholic Acid with 100 ml. of water for 2 minutes: the mixture is odorless.

Barium—Add to the mixture obtained in the test for *Odor on boiling* 2 ml. of hydrochloric acid, and again boil for 2 minutes. Cool, filter, and wash with water until the filtrate measures 100 ml. To 10 ml. of the filtrate add 1 ml. of diluted sulfuric acid: no turbidity is produced.

Heavy metals, *Method II,* page 806—The heavy metals limit for Dehydrocholic Acid is 20 parts per million.

Salmonella, page 862—The test for *Salmonella* in Dehydrocholic Acid is negative.

Assay—Transfer about 500 mg. of Dehydrocholic Acid, accurately weighed, to a 300-ml. conical flask, add 60 ml. of neutralized alcohol, and warm on a steam bath until solution is effected. Cool, add phenolphthalein T.S. and 20 ml. of water, and titrate with 0.1*N* sodium hydroxide, adding 100 ml. of water shortly before the end-point is reached. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 40.25 mg. of $C_{24}H_{34}O_5$.

Packaging and storage—Preserve Dehydrocholic Acid in well-closed containers.

CATEGORY—Choleretic.
USUAL DOSE—**500 mg.** three times a day.
USUAL DOSE RANGE—**250** to **750 mg.**

Dehydrocholic Acid Tablets

Dehydrocholic Acid Tablets contain not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{24}H_{34}O_5$.

Identification—Mix a quantity of finely powdered Dehydrocholic Acid Tablets, equivalent to about 500 mg. of dehydrocholic acid, with 15 ml. of water, and add slowly, with stirring, 2 ml. of sodium carbonate T.S. Filter, and add to the filtrate diluted hydrochloric acid (about 2 ml.), dropwise, until no more precipitate is formed. Filter the precipitate, wash with small portions of cold water until free from chloride, and dry at 105° for 2 hours: the dehydrocholic acid so obtained conforms to the *Melting range* and *Specific rotation* requirements under *Dehydrocholic Acid,* page 198.

Disintegration, page 878—The disintegration time limit for Dehydrocholic Acid Tablets is 30 minutes.

Weight variation, page 901—Dehydrocholic Acid Tablets meet the requirements of the weight variation test for tablets.

Salmonella, page 862—The test for *Salmonella* in Dehydrocholic Acid Tablets is negative.

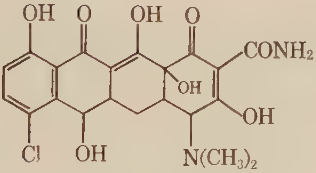
Assay—Weigh and finely powder not less than 20 Dehydrocholic Acid Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg. of dehydrocholic acid, to a 300-ml. conical flask, add 60 ml. of neutralized alcohol, and warm on a steam bath for 10 minutes. Cool, add phenolphthalein T.S. and 20 ml. of water, and titrate with 0.1 *N* sodium hydroxide, adding 100 ml. of water shortly before the end-point is reached. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 40.25 mg. of $C_{24}H_{34}O_5$.

Packaging and storage—Preserve Dehydrocholic Acid Tablets in well-closed containers.

Tablets available—Dehydrocholic Acid Tablets usually available contain the following amount of dehydrocholic acid: 250 mg.

CATEGORY and DOSE—See Dehydrocholic Acid.

Demeclocycline



7-Chloro-6-demethyltetracycline

7-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxo-2-naphthacenecarboxamide

$C_{21}H_{21}ClN_2O_8$ Mol. wt. 464.86

Demeclocycline contains not less than 97.0 percent of $C_{21}H_{21}ClN_2O_8$, calculated on the anhydrous basis. Demeclocycline conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Demeclocycline occurs as a yellow, crystalline powder. It is odorless and has a bitter taste. Its 1 in 100 solution has a pH of about 4.8.

Solubility—Demeclocycline is sparingly soluble in water and is soluble in alcohol. It readily dissolves in diluted hydrochloric acid and in alkaline solutions.

Packaging and storage—Preserve Demeclocycline in tight containers, protected from light.

CATEGORY—Antibacterial.

USUAL DOSE—**600 mg.** daily in 4 divided doses of 150 mg. each or 2 divided doses of 300 mg. each.

USUAL DOSE RANGE—**150** to **900 mg.** a day.

Demeclocycline for Oral Suspension

Demeclocycline for Oral Suspension is a dry mixture of demeclocycline and may contain one or more suitable colors, flavors, buffers, and preservatives. It contains demeclocycline equivalent to not less than 85.0 percent of the labeled amount of $C_{21}H_{21}ClN_2O_8 . HCl$, and conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Demeclocycline for Oral Suspension in tight containers, protected from light.

Size available—Demeclocycline for Oral Suspension usually available contains an amount of demeclocycline equivalent to 900 mg. of demeclocycline hydrochloride in a 60-ml. container.

CATEGORY and DOSE—See Demeclocycline.

Demeclocycline Oral Suspension

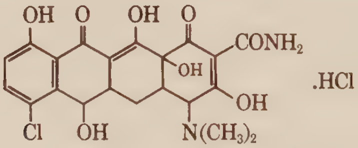
Demeclocycline Oral Suspension contains demeclocycline equivalent to not less than 85.0 percent of the labeled amount of $C_{21}H_{21}ClN_2O_8.HCl$. Demeclocycline Oral Suspension conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Demeclocycline Oral Suspension in tight containers, protected from light.

Suspension available—Demeclocycline Oral Suspension usually available contains an amount of demeclocycline equivalent to 75 mg. of demeclocycline hydrochloride in each 5 ml.

CATEGORY and DOSE—See Demeclocycline.

Demeclocycline Hydrochloride*



7-Chloro-6-demethyltetracycline Hydrochloride

7-Chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxo-2-naphthacenecarboxamide Monohydrochloride

$C_{21}H_{21}ClN_2O_8.HCl$ Mol. wt. 501.32

Demeclocycline Hydrochloride contains not less than 90.0 percent of $C_{21}H_{21}ClN_2O_8.HCl$. Demeclocycline Hydrochloride conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Demeclocycline Hydrochloride occurs as a yellow, crystalline powder. It is odorless and has a bitter taste. The pH of a 1 in 100 solution is about 2.5.

Solubility—Demeclocycline Hydrochloride is sparingly soluble in water and is slightly soluble in alcohol. It is sparingly soluble in solutions of alkali hydroxides and carbonates. It is practically insoluble in acetone and in chloroform.

Packaging and storage—Preserve Demeclocycline Hydrochloride in tight containers, protected from light.

CATEGORY—Antibacterial.

USUAL DOSE—**600 mg.** daily in 4 divided doses of 150 mg. each or 2 divided doses of 300 mg. each.

USUAL DOSE RANGE—**150** to **900 mg.** per day.

Demeclocycline Hydrochloride Capsules

Demeclocycline Hydrochloride Capsules contain not less than 85.0 percent of the labeled amount of $C_{21}H_{21}ClN_2O_8.HCl$. Demeclocycline Hydrochloride Capsules conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Demeclocycline Hydrochloride Capsules in tight, light-resistant containers.

Capsules available—Demeclocycline Hydrochloride Capsules usually available contain the following amounts of demeclocycline hydrochloride: 75 and 150 mg.

CATEGORY and DOSE—See Demeclocycline Hydrochloride.

Demeclocycline Hydrochloride Tablets

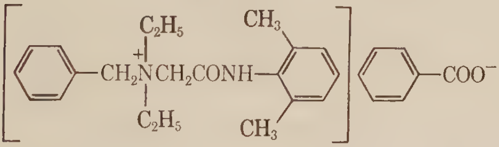
Demeclocycline Hydrochloride Tablets contain not less than 90.0 percent of the labeled amount of $C_{21}H_{21}ClN_2O_8.HCl$. Demeclocycline Hydrochloride Tablets conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Demeclocycline Hydrochloride Tablets in tight containers.

Tablets available—Demeclocycline Hydrochloride Tablets usually available contain the following amounts of demeclocycline hydrochloride: 75, 150, and 300 mg.

CATEGORY and DOSE—See Demeclocycline Hydrochloride.

Denatonium Benzoate



Benzyldiethyl[(2,6-xylylcarbamoyl)methyl]ammonium Benzoate

$C_{28}H_{34}N_2O_3$ Mol. wt. 446.59

Denatonium Benzoate, dried at 105° for 2 hours, contains not less than 99.5 percent and not more than 101.0 percent of $C_{28}H_{34}N_2O_3$.

Description—Denatonium Benzoate occurs as a white, odorless, crystalline powder. It has an intensely bitter taste.

Solubility—Denatonium Benzoate is soluble in water, freely soluble in alcohol and in chloroform, sparingly soluble in acetone, and practically insoluble in ether.

Identification—

A: Dissolve about 150 mg. of Denatonium Benzoate in 10 ml. of water and add 15 ml. of trinitrophenol T.S.: a yellow precipitate is formed.

B: Dissolve about 100 mg. of Denatonium Benzoate in 10 ml. of water, and add 20 ml. of diluted sulfuric acid and 15 ml. of ammonium reineckate T.S. Mix, filter through a sintered-glass crucible using gentle suction, and wash thoroughly with water. Remove as much water as possible with suction, and then dry in an oven at 105° for 1 hour. The denatonium reineckate so obtained melts at about 170°, page 814.

Melting range, *Class Ia,* page 815—

Denatonium Benzoate melts between 166° and 170°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Denatonium Benzoate, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Denatonium Benzoate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 10,000 solution of Denatonium Benzoate in water exhibits maxima and minima at the same wavelengths as that of NF Denatonium Benzoate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 263 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Denatonium Benzoate (1 in 10) is between 7.0 and 8.0.

Loss on drying, page 814—Dry Denatonium Benzoate at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Denatonium Benzoate yields not more than 0.1 percent of residue on ignition.

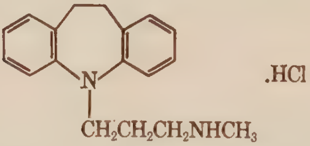
Chloride, page 784—Dissolve 350 mg. of Denatonium Benzoate in 9 ml. of water, add 1 ml. of nitric acid, and filter. A 1-ml. portion of the filtrate shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (0.2 percent).

Assay—Dissolve about 900 mg. of Denatonium Benzoate, previously dried at 105° for 2 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 44.66 mg. of $C_{28}H_{34}N_2O_3$.

Packaging and storage—Preserve Denatonium Benzoate in tight containers.

CATEGORY—Alcohol denaturant.

Desipramine Hydrochloride*



10,11-Dihydro-5-[3-(methylamino) propyl]-5*H*-dibenz[*b,f*]azepine Monohydrochloride

$C_{18}H_{22}N_2 . HCl$ Mol. wt. 302.85

Desipramine Hydrochloride, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{22}N_2 . HCl$.

Description—Desipramine Hydrochloride occurs as a white to off-white crystalline powder.

Solubility—Desipramine Hydrochloride is soluble in water and in alcohol. It is freely soluble in methanol and in chloroform, and is insoluble in ether.

Identification—

A: Add about 5 mg. of Desipramine Hydrochloride to 2 ml. of nitric acid on a spot plate: an intense blue color is produced.

B: A solution of Desipramine Hydrochloride in alcohol (1 in 20) responds to the tests for *Chloride*, page 808.

Melting range, *Class Ia,* page 815—Desipramine Hydrochloride melts within a range of 5° between 208° and 218°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Desipramine Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Desipramine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 3 in 100,000 solution of Desipramine Hydrochloride in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Desipramine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 251 mμ, do not differ by more than 2 percent.

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* Patent pending. See notice, page ii.

Loss on drying, page 814—Dry Desipramine Hydrochloride in vacuum at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Desipramine Hydrochloride yields not more than 0.1 percent of residue on ignition. Retain the residue for the *Heavy metals test.*

Heavy metals, page 806—To the residue obtained in the test for *Residue on ignition* add 1 ml. of hydrochloric acid and 0.5 ml. of nitric acid, and evaporate on a steam bath to dryness. Add 2 ml. of diluted acetic acid, digest on a steam bath for 5 minutes, filter if necessary, and wash the residue with sufficient water to make 25 ml.: the heavy metals limit for Desipramine Hydrochloride is 10 parts per million.

Iminodibenzyl—

Standard preparation—Transfer 12.5 mg. of NF Iminodibenzyl Reference Standard to a 25-ml. volumetric flask, dissolve in alcohol, dilute to volume with alcohol, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Transfer 1.0 ml. of this solution to a low-actinic 25-ml. volumetric flask, add 10 ml. of hydrochloric acid-alcohol (1:1), and mix.

Test preparation—Transfer 50.0 mg. of Desipramine Hydrochloride to a low-actinic 25-ml. volumetric flask, add 10 ml. of hydrochloric acid-alcohol (1:1), and mix.

Procedure—To each flask and to a third flask containing 10 ml. of hydrochloric acid-alcohol (1:1) to serve as the blank, add slowly 5 ml. of a 0.4 percent (v/v) solution of furfuraldehyde in alcohol, mix, then add 5 ml. of hydrochloric acid, and allow the flasks to stand for 3 hours in a constant-temperature bath at 25°. Dilute each flask to volume with hydrochloric acid-alcohol (1:1), and mix. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 565 mμ, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance of the solution from the *Test preparation* is not greater than that from the *Standard preparation* (0.1 percent).

Assay—Dissolve about 300 mg. of Desipramine Hydrochloride, previously dried at 105° for 2 hours and accurately weighed, in 100 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S., and titrate potentiometrically with 0.1 *N* perchloric acid in glacial acetic acid using glass and calomel electrodes. Each ml. of 0.1 *N* perchloric acid is equivalent to 30.29 mg. of $C_{18}H_{22}N_2.HCl$.

Packaging and storage—Preserve Desipramine Hydrochloride in tight containers.

CATEGORY—Antidepressant.

USUAL DOSE—**150 mg.** per day in divided doses.

USUAL DOSE RANGE—**50** to **200 mg.** per day.

Desipramine Hydrochloride Capsules

Desipramine Hydrochloride Capsules contain not less than 92.0 percent and not more than 108.0 percent of the labeled amount of $C_{18}H_{22}N_2.HCl$.

Identification—Mix the contents of Desipramine Hydrochloride Capsules, equivalent to about 125 mg. of desipramine hydrochloride, with 10 ml. of chloroform, stir for 5 minutes, and filter. Evaporate the chloroform on a steam bath to a volume of about 4 ml., add ether until the solution becomes turbid, then heat slightly on the steam bath to remove the turbidity, and cool: the crystals of desipramine hydrochloride so obtained, when filtered and dried at 100° for 30 minutes, respond to the *Identification tests* and meet the requirements for *Melting range* under *Desipramine Hydrochloride,* page 202.

Content uniformity, *Method II*, page 798—Desipramine Hydrochloride Capsules meet the requirements of the content uniformity test for capsules, using the following special procedure: Quantitatively transfer the contents of a capsule and the capsule shell to a 100-ml. volumetric flask with the aid of 70 ml. of 30 percent alcohol, and shake for 30 minutes using a mechanical shaker that provides vigorous agitation. Dilute to volume with 30 percent alcohol, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise with 30 percent alcohol to provide a solution containing approximately 25 mcg. of desipramine hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Desipramine Hydrochloride Reference Standard, in the same medium, at a concentration of about 25 mcg. per ml., in 1-cm. cells, at the maximum at about 251 mμ, with a suitable spectrophotometer, using 30 percent alcohol as the blank. Calculate the quantity, in mg., of $C_{18}H_{22}N_2.HCl$ in the capsule by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of desipramine hydrochloride in the capsules; D is the exact concentration, in mcg. per ml., of desipramine hydrochloride in the sample solution based upon the labeled quantity per capsule and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Transfer as completely as possible the contents of not less than 20 Desipramine Hydrochloride Capsules to a tared weighing bottle, and weigh. Transfer an accurately weighed quantity of the powder, equivalent to about 250 mg. of desipramine hydrochloride, to a 250-ml. volumetric flask, add about 100 ml. of hydrochloric acid solution (4 in 100), and shake mechanically for 1 hour. Dilute to volume with hydrochloric acid solution (4 in 100), mix, and filter, discarding the first 20 ml. of filtrate. Transfer 5.0 ml. of the subsequent filtrate to a separator, add 60 ml. of sodium hydroxide T.S., and extract with four 20-ml. portions of ether, shaking each portion for 2 minutes and collecting the extracts in a second separator. Extract the combined ether extracts with four 30-ml. portions of hydrochloric acid solution (4 in 100), combine the acid extracts in a 200-ml. volumetric flask, dilute to volume with hydrochloric acid solution (4 in 100), and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Desipramine Hydrochloride Reference Standard, in the same medium, at a concentration of about 25 mcg. per ml., in 1-cm. cells, at the maximum at about 251 mμ, with a suitable spectrophotometer, using hydrochloric acid solution (4 in 100) as the blank. Calculate the quantity, in mg., of $C_{18}H_{22}N_2.HCl$ in the portion of the Capsules taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Desipramine Hydrochloride Capsules in tight containers.

Capsules available—Desipramine Hydrochloride Capsules usually available contain the following amount of desipramine hydrochloride: 25 mg.

CATEGORY and DOSE—See Desipramine Hydrochloride.

Desipramine Hydrochloride Tablets

Desipramine Hydrochloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{18}H_{22}N_2.HCl$.

Identification—Finely powder a number of Desipramine Hydrochloride Tablets, equivalent to about 350 mg. of desipramine hydrochloride, and triturate the powder with 15 ml. of chloroform. Filter the chloroform extract through paper into a wide-mouth test tube, and evaporate the filtrate to about 3 ml. Carefully add ether until the liquid becomes turbid, heat to produce a clear solution, then cool, and allow to stand. Collect the crystals, wash with ether, and dry at 80° in vacuum for 30 minutes: the desipramine hydrochloride so obtained responds to the *Identification tests* and meets the requirements for *Melting range* under *Desipramine Hydrochloride*, page 202.

Disintegration, page 878—The disintegration time limit for Desipramine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Desipramine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask, add 50 ml. of 0.1 *N* hydrochloric acid, and shake mechanically for 15 minutes. Dilute to volume with 0.1 *N* hydrochloric acid, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise with 0.1 *N* hydrochloric acid to provide a solution containing approximately 25 mcg. of desipramine hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Desipramine Hydrochloride Reference Standard, in the same medium, at a concentration of about 25 mcg. per ml., in 1-cm. cells, at the maximum at about 251 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{18}H_{22}N_2.HCl$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity in mg., of desipramine hydrochloride in the tablet; D is the exact concentration, in mcg. per ml., of desipramine hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Desipramine Hydrochloride Tablets. Weigh accurately a portion of the powder, equivalent to about 100 mg. of Desipramine Hydrochloride, and transfer with the aid of 60 ml. of 0.1 *N* hydrochloric acid to a 100-ml. volumetric flask. Shake for 30 minutes, add 0.1 *N* hydrochloric acid to volume, mix, and filter, rejecting the first 10 ml. of filtrate. Transfer 15.0 ml. of the subsequent filtrate to a separator, add 10 g. of anhydrous potassium carbonate, mix to dissolve, and extract with one 40-ml. portion of ether followed by three successive extractions with 25-ml. portions of ether. Add 2 ml. of 0.1 *N* hydrochloric acid to the combined ether extracts, and evaporate the ether under vacuum in a water bath at about 45°. Transfer the residue with the aid of 0.1 *N* hydrochloric acid to a 500-ml. volumetric flask, add 0.1 *N* hydrochloric acid to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Desipramine Hydrochloride Reference Standard, in the same medium at a concentration of about 30 mcg. per ml., at the maximum at about 251 mμ, in 1-cm. cells, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{18}H_{22}N_2.HCl$, in the portion of Tablets taken by the formula $3.333C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Desipramine Hydrochloride Tablets in tight containers.

Tablets available—Desipramine Hydrochloride Tablets usually available contain the following amounts of desipramine hydrochloride: 25 and 50 mg.

Category and Dose—See Desipramine Hydrochloride.

Desoxycorticosterone Acetate Pellets

Desoxycorticosterone Acetate Pellets are sterile pellets composed of desoxycorticosterone acetate in compressed form, without the presence of any binder, diluent, or excipient. They contain not less than 97.0 percent and not more than 103.0 percent of $C_{23}H_{32}O_4$.

Solubility in alcohol—A solution of 25 mg. of powdered Desoxycorticosterone Acetate Pellets in 1 ml. of alcohol is clear and practically free from insoluble residue.

Melting range, *Class Ia,* page 815—Desoxycorticosterone Acetate Pellets melt between 155° and 161°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Desoxycorticosterone Acetate Pellets exhibits maxima only at the same wavelengths as that of USP Desoxycorticosterone Acetate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Desoxycorticosterone Acetate Pellets in alcohol exhibits maxima and minima at the same wavelengths as that of USP Desoxycorticosterone Acetate Reference Standard, similarly measured, and the respective absorptivities at the point of maximum absorption, occurring at about 240 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Desoxycorticosterone Acetate Pellets, determined in a solution in dioxane containing 100 mg. of desoxycorticosterone acetate in each 10 ml., is not less than +168° and not more than +176°.

Sterility—Desoxycorticosterone Acetate Pellets meet the requirements under *Sterility Tests,* page 874.

Weight variation—Weigh 5 Desoxycorticosterone Acetate Pellets singly, and calculate the average weight. The average weight is not less than 95 percent and not more than 105 percent of the labeled weight of $C_{23}H_{32}O_4$, and each pellet weighs not less than 90 percent and not more than 110 percent of the labeled weight of $C_{23}H_{32}O_4$.

Assay—

Standard preparation—Prepare as directed for the *Standard preparation* under *Steroid Assay,* page 876, using USP Desoxycorticosterone Acetate Reference Standard.

Assay preparation—Weigh and finely powder not less than 10 Desoxycorticosterone Acetate Pellets. Weigh accurately about 100 mg. of the powder, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Pipet 5.0 ml. of this solution into a 250-ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay,* page 876. Calculate the quantity in mg. of $C_{23}H_{32}O_4$ in the portion of the Pellets taken by the formula $10C \times (A_U/A_S)$.

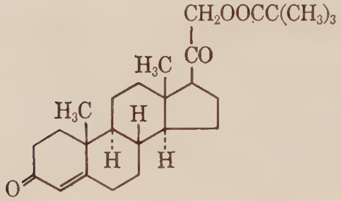
Packaging and storage—Preserve Desoxycorticosterone Acetate Pellets in tight containers suitable for maintaining sterile contents, holding one Pellet each.

Pellets available—Desoxycorticosterone Acetate Pellets usually available contain the following amounts of desoxycorticosterone acetate: 75 and 125 mg.

CATEGORY—Mineralcorticoid.

USUAL DOSE—Implantation, **75 mg.** per mg. of daily intramuscular dose.

Desoxycorticosterone Pivalate*



21-Hydroxypregn-4-ene-3,20-dione Pivalate

$C_{26}H_{38}O_4$ Mol. wt. 414.59

Desoxycorticosterone Pivalate contains not less than 97.0 percent and not more than 103.0 percent of $C_{26}H_{38}O_4$, calculated on the dried basis.

Description—Desoxycorticosterone Pivalate occurs as a white, or creamy white, crystalline powder. It is odorless and is stable in air.

Solubility—Desoxycorticosterone Pivalate is practically insoluble in water. It is slightly soluble in alcohol, in methanol, in ether, and in vegetable oils. It is sparingly soluble in acetone, and soluble in dioxane.

Identification—Dissolve about 5 mg. of Desoxycorticosterone Pivalate in 2 ml. of sulfuric acid: the solution is yellowish, with a greenish fluorescence. Dilute the solution with 2 ml. of water: the color changes to a dark red-blue, and on further dilution with 2 ml. of water it is discharged.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Desoxycorticosterone Pivalate, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Desoxycorticosterone Pivalate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Desoxycorticosterone Pivalate in methanol exhibits maxima and minima at the same wavelengths as that of NF Desoxycorticosterone Pivalate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 241 mμ, do not differ by more than 3 percent.

Melting range, *Class Ia,* page 815—Desoxycorticosterone Pivalate melts between 200° and 206°.

Specific rotation, page 822—The specific rotation of Desoxycorticosterone Pivalate, calculated on the dried basis, determined in a solution in dioxane containing 100 mg. of Desoxycorticosterone Pivalate in each 10 ml., is between +153° and +161°.

Loss on drying, page 814—Dry Desoxycorticosterone Pivalate at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Desoxycorticosterone Pivalate Reference Standard to prepare a solution containing approximately 4 mg. per ml.

Test preparation—Weigh accurately about 40 mg. of Desoxycorticosterone Pivalate, previously dried at 105° for 2 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of benzene and ethyl acetate (4:3), and determining the absorbance at the maximum at about 240 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Desoxycorticosterone Pivalate taken: not more than 3 percent is found.

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* Patented. See notice, page ii.

Assay—

Standard preparation—Prepare as directed for *Standard preparation* under *Steroid Assay*, page 876, using NF Desoxycorticosterone Pivalate Reference Standard.

Assay preparation—Weigh accurately about 100 mg. of Desoxycorticosterone Pivalate, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Pipet 5.0 ml. of this solution into a 250-ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered 50-ml. conical flask.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{26}H_{38}O_4$ in the portion of Desoxycorticosterone Pivalate taken by the formula $10C \times (A_U/A_S)$.

Packaging and storage—Preserve Desoxycorticosterone Pivalate in well-closed, light-resistant containers.

CATEGORY—Mineralcorticoid.

USUAL DOSE RANGE—Intramuscular, **50** to **100 mg.**, repeated in not less than 30 days.

Sterile Desoxycorticosterone Pivalate Suspension

Sterile Desoxycorticosterone Pivalate Suspension is a sterile suspension of desoxycorticosterone pivalate in an aqueous medium. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{26}H_{38}O_4$.

Identification—Centrifuge a portion of Sterile Desoxycorticosterone Pivalate Suspension, decant the supernatant liquid, wash the residue by stirring with several successive portions of water, centrifuging and decanting each time, and finally dry the residue at 105°: the desoxycorticosterone pivalate so obtained melts between 198° and 204° as determined by the method for *Class Ia*, page 815, and responds to the *Identification test* under *Desoxycorticosterone Pivalate*, page 206.

pH, page 824—The pH of Sterile Desoxycorticosterone Pivalate Suspension is between 5.0 and 7.0.

Other requirements—Sterile Desoxycorticosterone Pivalate Suspension meets the requirements under *Injections*, page 810.

Assay—Transfer to a 50-ml. volumetric flask an accurately measured volume of Sterile Desoxycorticosterone Pivalate Suspension, equivalent to about 50 mg. of desoxycorticosterone pivalate, add water to volume, and mix. Place about 3 mm. of glass wool in the bottom of a chromatographic tube, about 200 mm. long and about 25 mm. in internal diameter, and cover with a well-packed mixture of 2 g. of purified siliceous earth and 1 ml. of water. Pipet 5.0 ml. of the diluted suspension into a beaker containing 8 g. of purified siliceous earth, mix, and add to the prepared chromatographic tube, packing uniformly. Rinse the beaker with a mixture of 1 g. of purified siliceous earth and 0.5 ml. of water, add to the tube, and cover with a 2-mm. layer of glass wool. Pour 120 ml. of water-saturated chloroform, in divided portions, onto the column, collecting about 98 ml. of eluate in a 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Pipet 5.0 ml. of this solution into a glass-stoppered, 50-ml. flask, evaporate the solution to dryness on a steam bath, and dissolve the residue in 25.0 ml. of methanol. Concomitantly determine the absorbance of this solution and of a solution of NF Desoxycorticosterone Pivalate Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{26}H_{38}O_4$ in each ml. of the Suspension taken by the formula $5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration of the standard solution, in mcg. per ml., V is the volume, in ml., of the Suspension taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Sterile Desoxycorticosterone Pivalate Suspension in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

Suspension available—Sterile Desoxycorticosterone Pivalate Suspension usually available contains the following amount of desoxycorticosterone pivalate: 100 mg. in 4 ml.

CATEGORY and DOSE—See Desoxycorticosterone Pivalate.

Dexamethasone Aerosol

Dexamethasone Aerosol is dexamethasone in a suitable lotion base mixed with fluorocarbon propellants in a pressurized container. Dexamethasone Aerosol delivers not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{29}FO_5$.

Identification—Evaporate on a steam bath just to dryness 5 ml. of the *Assay preparation* obtained as directed in the *Assay*, and dissolve the residue in 1 ml. of chloroform. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 100 µl. of this solution and 10 µl. of a chloroform solution of USP Dexamethasone Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and diethylamine (2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a heat lamp until spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Delivery rate—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using USP Dexamethasone Reference Standard.

Test preparation—Allow the Dexamethasone Aerosol container to equilibrate at 25°. Shake gently and invert, immersing the valve in about 75 ml. of alcohol contained in a 400-ml. beaker. Actuate the valve by pushing against the bottom of the beaker, and allow to spray for 10 seconds, accurately timed. Transfer the alcohol solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Transfer 20.0 ml. of this solution to a 50-ml. glass-stoppered flask.

Procedure—Proceed as directed under *Steroid Assay*, page 876, except allow to stand in the dark for 45 minutes. Calculate the quantity, in mg., of $C_{22}H_{29}FO_5$ delivered per second by the formula $0.01C \times (A_U/A_S)$. Dexamethasone is delivered at a rate of not less than 0.060 mg. and not more than 0.090 mg. per second.

Other requirements—Dexamethasone Aerosol meets the requirements for *Leak Testing* and *Pressure Testing* under *Aerosols*, page 770.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using USP Dexamethasone Reference Standard.

Assay preparation—Shake the Dexamethasone Aerosol container gently and invert, immersing the valve in about 75 ml. of alcohol contained in a 400-ml. beaker. Actuate the valve by pushing against the bottom of the beaker. Remove the container at 15-second intervals, shake gently, and allow the container to warm to room temperature. Continue spraying until the container is exhausted. Transfer the alcohol solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Dilute an accurately measured volume of this solution, equivalent to about 1 mg. of dexamethasone, to 100.0 ml. with alcohol, and mix. Transfer 20.0 ml. of this solution to a 50-ml. glass-stoppered flask.

Procedure—Proceed as directed under *Steroid Assay*, page 876, except allow to stand in the dark for 45 minutes. Calculate the quantity, in mg., of $C_{22}H_{29}FO_5$ per container by the formula $10 \times (C/V) \times (A_U/A_S)$, in which V is the volume, in ml., of sample solution taken for the second dilution.

Packaging and storage—Preserve Dexamethasone Aerosol in pressurized containers, and protect from excessive heat.

Aerosols available—Dexamethasone Aerosol usually available contains the following amounts of dexamethasone: 10 mg. per 90-g. container; 3.3 mg. per 30-g. container.

CATEGORY—Glucocorticoid.

FOR EXTERNAL USE—Spray affected area for 1 to 2 seconds two or three times a day.

Dexamethasone Elixir

Dexamethasone Elixir contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{29}FO_5$.

Identification—Evaporate 50 ml. of the *Assay preparation* from the *Assay* on a steam bath just to dryness, and dissolve the residue in 1 ml. of chloroform. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm.

layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a chloroform solution of USP Dexamethasone Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and diethylamine (2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear. The R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using USP Dexamethasone Reference Standard.

Assay preparation—Transfer an accurately measured volume of Dexamethasone Elixir, equivalent to about 1 mg. of dexamethasone, to a separator, and add water to make about 15 ml. Extract the dexamethasone completely, using four 20-ml. portions of chloroform, filtering each portion through chloroform-washed cotton into a 100-ml. volumetric flask, add chloroform to volume, and mix. Pipet 20.0 ml. of the solution into a glass-stoppered, 50-ml. conical flask, evaporate the chloroform on a steam bath just to dryness, cool, and dissolve the residue in 20.0 ml. of alcohol.

Procedure—Proceed as directed under *Steroid Assay*, page 876, except allow to stand in the dark for 45 minutes. Calculate the quantity, in mg. per ml., of $C_{22}H_{29}FO_5$ in the Elixir by the formula $0.1 \times (C/V) \times (A_U/A_S)$, in which V is the volume, in ml., of the Elixir taken.

Alcohol content, page 772—Dexamethasone Elixir contains from 3.8 to 5.7 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Dexamethasone Elixir in tight containers.

Elixir available—Dexamethasone Elixir usually available contains the following amount of dexamethasone: 500 mcg. in 5 ml.

Category—Glucocorticoid.

Usual dose of dexamethasone—**750 mcg.** two to four times a day.

Usual dose range of dexamethasone—**500 mcg.** to **6 mg.** daily.

Dexamethasone Sodium Phosphate Cream

Dexamethasone Sodium Phosphate Cream contains an amount of $C_{22}H_{28}FNa_2O_8P$ (dexamethasone sodium phosphate) equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{22}H_{30}FO_8P$ (dexamethasone phosphate).

Identification—

A: Heat 1 ml. of the *Assay preparation* prepared as directed in the *Assay*, with 5 ml. of phenylhydrazine reagent (prepared as described under *Assay*) at 70° for 2 hours: a yellow color develops.

B: Place 5 ml. of the *Assay preparation* prepared as directed in the *Assay*, in a 50-ml. glass-stoppered tube. Incubate at 37° for 45 minutes with 5 ml. of alkaline phosphatase solution, prepared by dissolving 50 mg. of alkaline phosphatase in 50 ml. of a buffer solution (pH = 9.0) made by dissolving 3.1 g. of boric acid, 203 mg. of magnesium chloride, and 860 mg. of sodium hydroxide in sufficient water to make 1000 ml. After the incubation add 25 ml. of methylene chloride, and shake for two minutes. Evaporate 15 ml. of the methylene chloride extract to dryness, dissolve the residue in 1 ml. of methylene chloride, and apply 5 µl. of the solution to a thin-layer chromatography plate coated with a 0.25-mm. layer of silica gel G. Apply to the same plate 5 µl. of a methylene chloride solution containing 300 mcg. per ml. of USP Dexamethasone Reference Standard. Develop the chromatogram in a tank completely lined with a strip of filter paper 18 cm. wide, the developing solvent consisting of a mixture of chloroform, acetone, and water (50:50:1). When the solvent front has ascended 15 cm. from the starting line, remove the plate from the tank, allow it to dry, and spray it with sulfuric acid solution (1 in 2). Heat at 105° until brown or black spots appear. The R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Weight variation, page 901—Dexamethasone Sodium Phosphate Cream meets the requirements of the weight variation test for creams.

Assay—

Standard preparation—Transfer about 120 mg. of USP Dexamethasone Sodium Phosphate Reference Standard, equivalent to about 100 mg. of dexamethasone phosphate, accurately weighed, to a 100-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix. Transfer 10.0 ml. of the solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer an accurately weighed portion of Dexamethasone Sodium Phosphate Cream, equivalent to about 1 mg. of dexamethasone phosphate, to a small separator containing about 7 ml. of sodium chloride solution (1 in 10). Add 25 ml. of methylene chloride, agitate to disperse the cream, allow the methylene chloride phase to separate, and discard it. Repeat the extraction with 25 ml. of methylene chloride, again discarding the methylene chloride extract. Transfer the aqueous phase to a 10-ml. volumetric flask, rinse the separator with 2 ml. of water, adding the rinsings to the flask, dilute to volume with water, and mix.

Procedure—Pipet 2.0 ml. each of the *Standard preparation*, the *Assay preparation*, and water into separate glass-stoppered tubes. Add to each tube 5.0 ml. of freshly prepared phenylhydrazine reagent, consisting of 40 ml. of water, 60 ml. of sulfuric acid, 50 ml. of isopropyl alcohol, and 65 mg. of phenylhydrazine hydrochloride. Stopper loosely and place in a water bath at 60° for 2 hours, and cool. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at 410 mμ, with a suitable spectrophotometer, using the reagent blank to set the instrument. Record the absorbance of the solution from the *Standard Preparation* as A_S and that from the *Assay Preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{30}FO_8P$ in the portion of the Cream taken by the formula $0.01C \times 0.9148 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Dexamethasone Sodium Phosphate Reference Standard in the *Standard preparation*, calculated on the water-free and alcohol-free basis, and 0.9148 is the factor for converting dexamethasone sodium phosphate to dexamethasone phosphate.

Packaging and storage—Preserve Dexamethasone Sodium Phosphate Cream in collapsible tubes, or in tight containers.

Cream available—Dexamethasone Sodium Phosphate Cream usually available contains 0.1 percent of dexamethasone phosphate.

CATEGORY—Glucocorticoid.

APPLICATION—Topically as a 0.1 percent cream to the affected area two or three times a day.

Dexamethasone Sodium Phosphate Ophthalmic Ointment

Dexamethasone Sodium Phosphate Ophthalmic Ointment contains an amount of $C_{22}H_{28}FNa_2O_8P$ (dexamethasone sodium phosphate) equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{22}H_{30}FO_8P$ (dexamethasone phosphate).

Identification—

A: Heat 1 ml. of the *Assay preparation*, prepared as directed in the *Assay*, with 5 ml. of phenylhydrazine reagent (prepared as described under *Assay*) at 70° for 2 hours: a yellow color develops.

B: Place 5 ml. of the *Assay preparation*, prepared as directed in the *Assay*, in a 50-ml. glass-stoppered tube. Incubate at 37° for 45 minutes with 5 ml. of alkaline phosphatase solution, prepared by dissolving 50 mg. of alkaline phosphatase in 50 ml. of a buffer solution (pH = 9.0) made by dissolving 3.1 g. of boric acid, 203 mg. of magnesium chloride, and 860 mg. of sodium hydroxide in sufficient water to make 1000 ml. After the incubation add 25 ml. of methylene chloride, and shake for 2 minutes. Evaporate 15 ml. of the methylene chloride extract to dryness, dissolve the residue in 1 ml. of methylene chloride, and apply 5 μl. of the solution to a thin-layer chromatographic plate coated with a 0.25-mm. layer of silica gel G. Apply to the same plate 5 μl. of a methylene chloride solution containing 300 mcg. per ml. of USP Dexamethasone Reference Standard. Develop the chromatogram in a tank completely lined with a strip of filter paper 18 cm. wide, the developing solvent consisting of a mixture of chloroform, acetone, and water (50:50:1). When the solvent front has ascended 15 cm. from the starting line, remove the plate from the tank, allow it to dry, and spray it with sulfuric acid solution (1 in 2). Heat at 105° until brown or black spots appear. The R_f value of the main spot from the sample solution corresponds to that obtained from the Reference Standard solution.

Weight variation, page 901—Dexamethasone Sodium Phosphate Ophthalmic Ointment meets the requirements of the weight variation test for ointments.

Metal particles—Dexamethasone Sodium Phosphate Ophthalmic Ointment meets the requirements of the test for *Metal Particles—Ophthalmic Ointments*, page 816.

Assay—

Standard preparation—Transfer about 120 mg. of USP Dexamethasone Sodium Phosphate Reference Standard, equivalent to about 100 mg. of dexamethasone phosphate, accurately weighed, to a 100-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix. Transfer 10.0 ml. of the solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer an accurately weighed portion of Dexamethasone Sodium Phosphate Ophthalmic Ointment, equivalent to about 1 mg. of dexamethasone phosphate, to a 125-ml. separator, add 25 ml. of methylene chloride to dissolve the Ointment, then add 10.0 ml. of water, and shake to extract the dexamethasone salt. Discard the methylene chloride, and again extract the aqueous layer with 25 ml. of methylene chloride, again discarding the methylene chloride.

Procedure—Pipet 2.0 ml. each of the *Standard preparation*, the *Assay preparation*, and water into separate glass-stoppered tubes. Add to each tube 5.0 ml. of freshly prepared phenylhydrazine reagent, consisting of 40 ml. of water, 60 ml. of sulfuric acid, 50 ml. of isopropyl alcohol, and 65 mg. of phenylhydrazine hydrochloride. Stopper loosely and place in a water bath at 60° for 2 hours, and cool. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at 410 mμ, with a suitable spectrophotometer, using the reagent blank to set the instrument Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{30}FO_8P$ in the portion of Ointment taken by the formula $0.01C \times 0.9148 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Dexamethasone Sodium Phosphate Reference Standard in the *Standard preparation*, calculated on the water-free and alcohol-free basis, and 0.9148 is the factor for converting dexamethasone sodium phosphate to dexamethasone phosphate.

Packaging and storage—Preserve Dexamethasone Sodium Phosphate Ophthalmic Ointment in collapsible ophthalmic ointment tubes.

Ointment available—Dexamethasone Sodium Phosphate Ophthalmic Ointment usually available contains 0.05 percent of dexamethasone phosphate.

CATEGORY—Glucocorticoid.

APPLICATION—Topically as a 0.05 percent ointment to the eye or ear one to three times a day.

Dexamethasone Sodium Phosphate Ophthalmic Solution

Dexamethasone Sodium Phosphate Ophthalmic Solution is a sterile solution of dexamethasone sodium phosphate in water. It contains an amount of $C_{22}H_{28}FNa_2O_8P$ (dexamethasone sodium phosphate) equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{22}H_{30}FO_8P$ (dexamethasone phosphate).

Identification—

A: Heat 1 ml. of the solution from the *Assay preparation* with 5 ml. of phenylhydrazine reagent (prepared as described under *Assay*) at 70° for 2 hours: a yellow color develops.

B: Place 5 ml. of the solution from the *Assay preparation* in a 50-ml. glass-stoppered tube. Incubate at 37° for 45 minutes with 5 ml. of alkaline phosphatase solution, prepared by dissolving 50 mg. of alkaline phosphatase in 50 ml. of a buffer solution (pH = 9.0) made by dissolving 3.1 g. of boric acid, 203 mg. of magnesium chloride, and 860 mg. of sodium hydroxide in sufficient water to make 1000 ml. After the incubation add 25 ml. of methylene chloride, and shake for two minutes. Evaporate 15 ml. of the methylene chloride extract to dryness, dissolve the residue in 1 ml. of methylene chloride, and apply 5 μl. of the solution to a thin-layer chromatography plate coated with a 0.25-mm. layer of silica gel G. Apply to the same plate 5 μl. of a methylene chloride solution containing 300 mcg. per ml. of USP Dexamethasone Reference Standard. Develop the chromatogram in a tank completely lined with a strip of filter paper 18 cm. wide, the developing solvent consisting of a mixture of chloroform, acetone, and water (50:50:1). When the solvent front has ascended 15 cm. from the starting line, remove the plate from the tank, allow it to dry, and spray it with sulfuric acid solution (1 in 2). Heat at 105° until brown or black spots appear. The R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

pH, page 824—The pH of Dexamethasone Sodium Phosphate Ophthalmic Solution is between 7.2 and 7.8.

Sterility—Dexamethasone Sodium Phosphate Ophthalmic Solution meets the requirements under *Sterility Tests*, page 874.

Assay—

Standard preparation—Transfer about 120 mg. of USP Dexamethasone Sodium Phosphate Reference Standard, equivalent to about 100 mg. of dexamethasone phosphate, accurately weighed, to a 100-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix. Transfer 10.0 ml. of the solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer an accurately measured volume of Dexamethasone Sodium Phosphate Ophthalmic Solution, equivalent to about 5 mg. of dexamethasone phosphate, to a 125-ml. separator containing about 25 ml. of water. Extract with two 25-ml. portions of methylene chloride, discarding the methylene chloride each time. Quantitatively transfer the aqueous phase to a 50-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Pipet 2.0 ml. each of the *Standard preparation*, the *Assay preparation*, and water into separate glass-stoppered tubes. Add to each tube 5.0 ml. of freshly prepared phenylhydrazine reagent, consisting of 40 ml. of water, 60 ml. of sulfuric acid, 50 ml. of isopropyl alcohol, and 65 mg. of phenylhydrazine hydrochloride. Stopper loosely and place in a water bath at 60° for 2 hours, and cool. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at 410 mμ with a suitable spectrophotometer, using the reagent blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{30}FO_8P$ in each ml. of the Solution taken by the formula $0.05 \times 0.9148 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Dexamethasone Sodium Phosphate Reference Standard in the *Standard preparation*, calculated on the water-free and alcohol-free basis, 0.9148 is the factor for converting dexamethasone sodium phosphate to dexamethasone phosphate, and V is the volume, in ml., of the Solution taken.

Packaging and storage—Preserve Dexamethasone Sodium Phosphate Ophthalmic Solution in tightly closed, light-resistant containers.

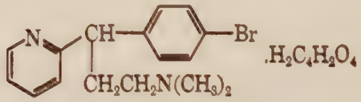
Solution available—Dexamethasone Sodium Phosphate Ophthalmic Solution usually available contains 0.1 percent of dexamethasone phosphate.

CATEGORY—Glucocorticoid.

APPLICATION—Topically as a 0.1 percent solution, 1 or 2 drops one to three times a day to the eye; 3 or 4 drops one to three times a day to the ear.

Dexamethasone Sodium Phosphate and Neomycin Sulfate Cream, page 473

Dexbrompheniramine Maleate*



(+)-2-[*p*-Bromo-α-[2-(dimethylamino)ethyl]benzyl]pyridine Maleate (1:1)

$C_{16}H_{19}BrN_2 . C_4H_4O_4$ Mol. wt. 435.32

Dexbrompheniramine Maleate, dried at 65° for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{16}H_{19}BrN_2 . C_4H_4O_4$.

Description—Dexbrompheniramine Maleate occurs as a white, odorless, crystalline powder. The pH of a 1 in 100 solution is about 5.

Solubility—Dexbrompheniramine Maleate is freely soluble in water, and is soluble in alcohol and in chloroform.

Identification—Dissolve about 500 mg. of Dexbrompheniramine Maleate in 5 ml. of water, add 2 ml. of stronger ammonia water, extract with three 5-ml. portions of chloroform, and discard the extracts. Evaporate the water solution to dryness, add several drops of diluted sulfuric acid to the residue, and then add 5 ml. of water, and extract the solution with four 25-ml. portions of ether. Filter the ether extracts through anhydrous sodium sulfate, previously moistened with ether, evaporate the filtrate to dryness in a current of air, and dry the residue at 105° for 1 hour: the maleic acid so obtained melts between 128° and 133°, page 814.

Melting range, *Class Ia*, page 815—Dexbrompheniramine Maleate melts between 103° and 113°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dexbrompheniramine Maleate, previously dried at 65°

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* Patented. See notice, page ii.

for 4 hours, exhibits maxima only at the same wavelengths as that of NF Dexbrompheniramine Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 30,000 solution of Dexbrompheniramine Maleate in methanol exhibits maxima and minima at the same wavelengths as that of NF Dexbrompheniramine Maleate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance occurring at about 261 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Dexbrompheniramine Maleate, calculated on the dried basis, determined in a solution in dimethylformamide, containing 500 mg. of Dexbrompheniramine Maleate in each 10 ml., is between +33.0° and +38.5°

Loss on drying, page 814—Dry Dexbrompheniramine Maleate at 65° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Dexbrompheniramine Maleate yields not more than 0.15 percent of residue on ignition.

Assay—Dissolve about 400 mg. of Dexbrompheniramine Maleate, previously dried at 65° for 4 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 21.77 mg. of $C_{16}H_{19}BrN_2 . C_4H_4O_4$.

Packaging and storage—Preserve Dexbrompheniramine Maleate in tight, light-resistant containers.

CATEGORY—Antihistaminic.
USUAL DOSE—**2 mg.** four times a day.
USUAL DOSE RANGE—**2** to **12 mg.** a day

Dexbrompheniramine Maleate Tablets

Dexbrompheniramine Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{19}BrN_2 . C_4H_4O_4$.

Identification—

A: Dexbrompheniramine Maleate Tablets meet the requirements under *Identification—Organic Nitrogenous Bases,* page 810.

B: Suspend completely a quantity of finely powdered Dexbrompheniramine Maleate Tablets, equivalent to 100 mg. of dexbrompheniramine maleate, in 100 ml. of 0.5 *N* hydrochloric acid. Adjust to pH 11 with stronger ammonia water, and extract with six 100-ml. portions of solvent hexane. Filter each extract through a pledget of glass wool, and evaporate the combined extracts on a steam bath just to the point where hexane vapors are no longer perceptible. Transfer the oily residue, with the aid of three 3-ml. portions of dimethylformamide, to a suitable glass-stoppered graduated cylinder, dilute to 10.0 ml. with dimethylformamide, and mix: the specific rotation of the dexbrompheniramine maleate in the Tablet powder taken is about +36°, page 822.

Disintegration, page 878—The disintegration time limit for Dexbrompheniramine Maleate Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Dexbrompheniramine Maleate Tablets meet the requirements of the content uniformity test for tablets.

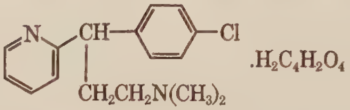
Assay—Weigh and finely powder not less than 20 Dexbrompheniramine Maleate Tablets. Weigh accurately a portion of the powder, equivalent to about 4 mg. of dexbrompheniramine maleate, mix well with 50 ml. of water for 10 minutes, adjust to pH 11 with sodium hydroxide solution (1 in 10), and cool to room temperature. Extract the mixture with two 75-ml. portions of solvent hexane. Extract the combined solvent hexane extracts with three 50-ml. portions of 0.1 *N* hydrochloric acid, combining the acid extracts in a 200-ml. volumetric flask. Dilute the acid extracts to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dexbrompheniramine Maleate Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 264 mμ, with a suitable spectrophotometer using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{19}BrN_2 . C_4H_4O_4$ in the portion of the Tablets taken by the formula $0.2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Dexbrompheniramine Maleate Tablets in tight, light-resistant containers.

Tablets available—Dexbrompheniramine Maleate Tablets usually available contain the following amount of dexbrompheniramine maleate: 2 mg.

CATEGORY and DOSE—See Dexbrompheniramine Maleate.

Dexchlorpheniramine Maleate*



(+)-2-[*p*-Chloro-*α*-[2-(dimethylamino)ethyl]benzyl]pyridine Maleate (1:1)

$C_{16}H_{19}ClN_2 . C_4H_4O_4$ Mol. wt. 390.87

Dexchlorpheniramine Maleate, dried at 65° for 4 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_{16}H_{19}ClN_2 . C_4H_4O_4$.

Description—Dexchlorpheniramine Maleate occurs as a white, odorless, crystalline powder.

Solubility—Dexchlorpheniramine Maleate is freely soluble in water. It is soluble in alcohol and in chloroform, and is slightly soluble in benzene and in ether.

Identification—Dissolve about 500 mg. of Dexchlorpheniramine Maleate in 5 ml. of water, add 2 ml. of stronger ammonia water, and extract the mixture with three 5-ml. portions of chloroform. Evaporate the water solution to dryness, add several drops of diluted sulfuric acid to the residue, then add 5 ml. of water, and extract the solution with four 25-ml. portions of ether. Evaporate the ether in a current of warm air: the residue of maleic acid so obtained melts between 128° and 133°, page 814.

Melting range, page 814—Dexchlorpheniramine Maleate melts between 110° and 115°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dexchlorpheniramine Maleate, previously dried at 65° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Dexchlorpheniramine Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 25,000 solution of Dexchlorpheniramine Maleate in water exhibits maxima and minima at the same wavelengths as that of NF Dexchlorpheniramine Maleate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 261 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Dexchlorpheniramine Maleate, calculated on the dried basis, determined in a solution in dimethylformamide, containing 500 mg. of Dexchlorpheniramine Maleate in each 10 ml., is between +39.5° and +43°.

pH, page 824—The pH of a solution of Dexchlorpheniramine Maleate (1 in 100) is between 4.0 and 5.0.

Loss on drying, page 814—Dry Dexchlorpheniramine Maleate at 65° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Dexchlorpheniramine Maleate yields not more than 0.15 percent of residue on ignition.

Assay—Dissolve about 400 mg. of Dexchlorpheniramine Maleate, previously dried at 65° for 4 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid, to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 19.54 mg. of $C_{16}H_{19}ClN_2 . C_4H_4O_4$.

Packaging and storage—Preserve Dexchlorpheniramine Maleate in tight, light-resistant containers.

CATEGORY—Antihistaminic.

USUAL DOSE—**2 mg.** three or four times a day.

USUAL DOSE RANGE—**1** to **2 mg.**

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* Patented. See notice, page ii.

Dexchlorpheniramine Maleate Syrup

Dexchlorpheniramine Maleate Syrup contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{19}ClN_2 . C_4H_4O_4$.

Identification—

A: Evaporate the remaining extract from the *Assay* to a small volume on a steam bath, then transfer it to a smaller, more suitable, vessel and evaporate just to the point where hexane vapors are no longer perceptible. Transfer the oily residue, with the aid of four 3-ml. portions of dimethylformamide, to a suitable glass-stoppered graduated cylinder, dilute to 15.0 ml. with dimethylformamide, and mix: the optical rotation of this solution in a 100-mm. tube, after correcting for the blank, is between +0.06° and +0.11° (*distinction from chlorpheniramine maleate*).

B: To a volume of Dexchlorpheniramine Maleate Syrup, equivalent to about 8 mg. of dexchlorpheniramine maleate, add sodium hydroxide solution (1 in 10) to produce a pH of about 11, cool the mixture, and extract with two 40-ml. portions of solvent hexane. Wash the combined extracts with 10 ml. of water, discard the water, and evaporate the hexane solution on a steam bath to dryness. Dissolve the residue in 5 ml. of alcohol, add 5 ml. of a saturated solution of picric acid in alcohol, heat on a steam bath for 5 minutes, and cool to room temperature. Filter the resulting yellow, crystalline precipitate on a sintered-glass crucible, wash with several portions of cold water followed by a small portion of cold alcohol, and dry the precipitate at 105° for 1 hour: the picrate so obtained melts between 196° and 204°, page 814. (*Caution: picrates may be explosive.*)

Assay—Transfer an accurately measured volume of Dexchlorpheniramine Maleate Syrup, equivalent to about 40 mg. of dexchlorpheniramine maleate, to a 250-ml. separator, add sodium hydroxide solution (1 in 10) to pH 11, and allow to cool to room temperature. Extract with five 50-ml. portions of solvent hexane. Collect the extracts in a 500-ml. separator and wash with two 10-ml. portions of water. Combine the water washes and extract them with two 20-ml. portions of solvent hexane, combining these extracts with the bulk of the water-washed extracts. Filter the combined hexane extracts through a solvent hexane-washed cotton pledget into a 500-ml. volumetric flask, dilute to volume with solvent hexane, and mix. Transfer 50.0 ml. of this solution to a 100-ml. beaker, and evaporate just to dryness on a steam bath. (Retain the remaining extract for *Identification test A.*) Dissolve the residue in 0.1 *N* hydrochloric acid and quantitatively transfer the solution, with the aid of 0.1 *N* hydrochloric acid, to a 100-ml. volumetric flask. Dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dexchlorpheniramine Maleate Reference Standard, in the same medium, at a concentration of about 40 mcg. per ml. in 1-cm. cells, at the maximum at about 265 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{19}ClN_2 . C_4H_4O_4$ in each ml. of the Syrup taken by the formula $(C/V) \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., V is the volume, in ml., of the Syrup taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Dexchlorpheniramine Maleate Syrup in well-closed, light-resistant containers.

Syrup available—Dexchlorpheniramine Maleate Syrup usually available contains the following amount of dexchlorpheniramine maleate: 2 mg. in 5 ml.

CATEGORY and DOSE—See Dexchlorpheniramine Maleate.

Dexchlorpheniramine Maleate Tablets

Dexchlorpheniramine Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{19}ClN_2 . C_4H_4O_4$.

Identification—

A: Dexchlorpheniramine Maleate Tablets meet the requirements under *Identification—Organic Nitrogenous Bases,* page 810.

B: Suspend completely a quantity of finely powdered Dexchlorpheniramine Maleate Tablets, equivalent to 150 mg. of dexchlorpheniramine maleate, in 100 ml. of diluted acetic acid, filter through a sintered-glass funnel into a suitable vessel, adjust the filtrate to pH 11 with sodium hydroxide solution (1 in 10), and extract the solution with six 100-ml. portions of solvent hexane. Concentrate the combined extracts to a small volume on a steam bath, transfer to a smaller, more suitable, vessel, and evaporate just to the point where hexane vapors are no longer perceptible. Transfer the oily residue, with the aid of four 3-ml. portions of dimethylformamide, to a suitable glass-stoppered graduated cylinder, dilute to 15.0 ml. with dimethylformamide, and mix: the optical rotation of this solution in a 100-mm. tube, after correcting for the blank, is between +0.24° and +0.35°.

Disintegration, page 878—The disintegration time limit for Dexchlorpheniramine Maleate Tablets is 15 minutes.

Content uniformity, *Method I,* page 799—Dexchlorpheniramine Maleate Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Dexchlorpheniramine Maleate Tablets. Weigh accurately a portion of the powder, equivalent to about 8 mg. of dexchlorpheniramine maleate, mix well with 50 ml. of water for 10 minutes, adjust to pH 11 with sodium hydroxide solution (1 in 10), and cool to room temperature. Extract the solution with two 75-ml. portions of solvent hexane. Extract the combined solvent hexane extracts with three 50-ml. portions of 0.1 *N* hydrochloric acid, combining the acid extracts in a 200-ml. volumetric flask. Dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dexchlorpheniramine Maleate Reference Standard, in the same medium, at a concentration of about 40 mcg. per ml. in 1-cm. cells, at the maximum at about 265 mμ, with a suitable spectrophotometer using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{19}ClN_2.C_4H_4O_4$ in the portion of the Tablets taken by the formula $0.2C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Dexchlorpheniramine Maleate Tablets in tight, light-resistant containers.

Tablets available—Dexchlorpheniramine Maleate Tablets usually available contain the following amount of dexchlorpheniramine maleate: 2 mg.

CATEGORY and DOSE—See Dexchlorpheniramine Maleate.

Dextriferron Injection

Dextriferron Injection is a sterile, colloidal solution prepared from a complex of ferric hydroxide with partially hydrolyzed dextrin in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of Fe (iron).

Description—Dextriferron Injection is a clear, dark brown liquid.

Identification—

A: To 1 ml. of Dextriferron Injection add 5 ml. of water and 1 ml. of stronger ammonia water: no precipitate is formed.

B: To 2 ml. of Dextriferron Injection add 10 ml. of 1 *M* sulfuric acid and 40 ml. of water. To 10 ml. of this solution add 1 ml. of potassium ferrocyanide T.S.: a dark blue precipitate is produced.

Specific gravity, page 866—The specific gravity of Dextriferron Injection is between 1.062 and 1.072 at 20°.

Viscosity, page 889—The viscosity of Dextriferron Injection is between 2.30 and 2.60 centipoises determined with the Ostwald-type viscosimeter at 20°.

Pyrogen—Dextriferron Injection meets the requirements of the *Pyrogen Test*, page 851, the test dose being 2 ml. per kg., with an injection rate of 2 ml. per minute.

pH, page 824—The pH of Dextriferron Injection is between 7.3 and 7.9.

Other requirements—Dextriferron Injection meets the requirements under *Injections*, page 810.

Nonvolatile residue—Accurately weigh the contents of one ampul of Dextriferron Injection in a platinum dish or crucible which has been previously dried and weighed. Evaporate on a steam bath to dryness, complete the drying in an oven at 105° for 15 hours, cool, and weigh: not less than 12 percent and not more than 16 percent of residue remains.

Assay for iron—

Standard preparation—Transfer to a 300-ml. Kjeldahl flask an accurately weighed portion of ferrous ammonium sulfate, equivalent to 100.0 mg. of iron (Fe), and proceed as directed under *Assay preparation*, beginning with "Add 10 ml. of nitric acid. . . . "

Assay preparation—Transfer an accurately weighed portion of Dextriferron Injection, equivalent to about 100 mg. of iron, to a 300-ml. Kjeldahl flask. Add 10 ml. of nitric acid, 10 ml. of sulfuric acid, and a few glass beads, and boil the solution gently until fumes of sulfur trioxide appear. Cool, add 3 ml. of nitric acid, and heat gently again until fumes of sulfur trioxide appear. Continue the addition of nitric acid, followed by gentle boiling, until the solution is clear and light yellow or green in color, then boil for an additional 30 minutes. Cool, cautiously add 100 ml. of water, and boil gently until solution is complete. Cool, transfer the solution to a 500-ml. volumetric flask, rinse the Kjeldahl flask with several small portions of water, dilute to volume with water, and mix. Pipet 5.0 ml. of the solution to a second 500-ml. volumetric flask, add 100 ml. of water and 1 g. of ascorbic acid, dilute to volume with water, and mix.

Procedure—Pipet 5.0-ml. portions of both the *Standard preparation* and the *Assay preparation* into clean, dry test tubes, and to each add 3.0 ml. of a solution of 2,2′-bipyridine in acetic acid (1 in 1500 ml. of dilute acetic acid [3.2 ml. of glacial acetic acid in 100 ml.]), mix, and allow to stand for 15 minutes. Concomitantly determine the absorbances of the *Assay preparation* and the *Standard preparation* at the wavelength of maximum absorbance at about 510 mμ, with a suitable spectrophotometer, using a mixture of 5 ml. of water and 3.0 ml. of 2,2′-bipyridine solution as the blank. Calculate the quantity, in mg., of Fe in the portion of the Injection taken by the formula 100 × (sp. gr./W) × (A_U/A_S), in which W is the weight, in g., of the Injection taken, sp. gr. is the value determined under *Specific gravity*, and A_U and A_S are the absorbances of the *Assay preparation* and *Standard preparation*, respectively.

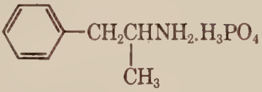
Packaging and storage—Preserve Dextriferron Injection in single-dose containers, preferably of Type I glass.

Injection available—Dextriferron Injection usually available contains the equivalent of 20 mg. of iron per ml. in 5-ml. containers.

Category—Source of iron.

Usual dose—Intravenous, initial trial dose of **1.5 ml.** (equivalent to 30 mg. of iron), then increase dose in increments of **1** to **1.5 ml.** (equivalent to 20 to 30 mg. of iron) per day until a daily dose of **5 ml.** (equivalent to 100 mg. of iron) is reached.

Dextroamphetamine Phosphate



(+)-α-Methylphenethylamine Phosphate (1:1)

$C_9H_{13}N . H_3PO_4$ Mol. wt. 233.21

Dextroamphetamine Phosphate, dried at 105° for 2 hours, contains not less than 98.5 percent and not more than 100.5 percent of $C_9H_{13}N . H_3PO_4$.

Description—Dextroamphetamine Phosphate occurs as a white, odorless, crystalline powder. It has a bitter taste.

Solubility—Dextroamphetamine Phosphate is soluble in water. It is slightly soluble in alcohol and is practically insoluble in benzene, in chloroform, and in ether.

Identification—

A: A solution of Dextroamphetamine Phosphate (1 in 20) responds to the tests for *Phosphate*, page 809.

B: To about 100 mg. of Dextroamphetamine Phosphate contained in a flask, add 5 ml. of water and 2 ml. of sodium hydroxide solution (2 in 5), then add benzoyl chloride, about 0.5 ml. at a time, shaking well after each addition, until no more precipitate forms upon further addition of the reagent. Collect the precipitate on a filter, wash it with about 15 ml. of cold water, and recrystallize it twice from diluted alcohol. The crystals of the benzoyl derivative of amphetamine so obtained, after drying at 80° for 2 hours, melt between 155° and 160°, page 814.

Specific rotation, page 822—The specific rotation of Dextroamphetamine Phosphate, previously dried at 105° for 2 hours, determined in a water solution containing 4 g. of Dextroamphetamine Phosphate in each 100 ml., is not less than +15° and not more than +19°.

pH, page 824—The pH of a solution of Dextroamphetamine Phosphate (1 in 20) is between 4.0 and 5.0.

Loss on drying, page 814—Dry Dextroamphetamine Phosphate at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Transfer about 1 g. of Dextroamphetamine Phosphate, accurately weighed, to a tared platinum crucible. Ignite carefully, using a low flame, until the sample is free of carbon, and then ignite strongly until no noticeable residue remains. Cool the crucible in a desiccator and weigh. Dextroamphetamine Phosphate yields not more than 0.1 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Dextroamphetamine Phosphate in sufficient water to make 20 ml., and add 5 ml. of 0.1 *N* hydrochloric acid: the heavy metals limit for Dextroamphetamine Phosphate is 30 parts per million.

Assay—

Standard preparation—Prepare as directed under *Amphetamine Assay*, page 776.

Assay preparation—Dissolve about 150 mg. of Dextroamphetamine Phosphate, previously dried at 105° for 2 hours and accurately weighed, in 25 ml. of hydrochloric acid solution (1 in 100) in a 50-ml. volumetric flask, dilute to volume with the solvent, and mix. Pipet 2.0 ml. of the solution into a 100-ml. beaker containing 3 g. of purified siliceous earth, and mix until a fluffy mixture is obtained.

Procedure—Proceed as directed under *Amphetamine Assay,* page 776. Calculate the quantity, in mg., of $C_9H_{13}N.H_3PO_4$ in the portion of Dextroamphetamine Phosphate taken by the formula $0.25C \times 1.266 \times [(A_{U257} - A_{U280})/(A_{S257} - A_{S280})]$, in which C is the exact concentration of USP Dextroamphetamine Sulfate Reference Standard, in mcg. per ml., in the *Standard preparation,* and 1.266 is the factor converting dextroamphetamine sulfate to dextroamphetamine phosphate.

Packaging and storage—Preserve Dextroamphetamine Phosphate in well-closed containers.

Category—Central stimulant.
Usual dose—**5 mg.** every 4 to 6 hours.
Usual dose range—**5** to **10 mg.**

Dextroamphetamine Phosphate Tablets

Dextroamphetamine Phosphate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_9H_{13}N.H_3PO_4$.

Identification—

A: Macerate a quantity of powdered Dextroamphetamine Phosphate Tablets, equivalent to 50 mg. of dextroamphetamine phosphate, with 5 ml. of water for 15 minutes, and filter into a small flask. To the filtrate add 1 ml. of sodium hydroxide solution (2 in 5), then add benzoyl chloride, about 0.5 ml. at a time, shaking well after each addition, until no more precipitate forms upon further addition of the reagent. Filter the precipitate, wash it with about 15 ml. of cold water and recrystallize it twice from diluted alcohol. The benzoyl derivative so obtained, after drying at 80° for 2 hours, melts between 155° and 160°, page 814.

B: Transfer the *Sample Solution,* prepared for the determination of absorbance in the *Assay,* to a separator, make it strongly alkaline with sodium hydroxide T.S., and extract with two 15-ml. portions of chloroform. Add to the chloroform extract 5 ml. of 0.1 N sulfuric acid, shake well, and heat gently until the chloroform is expelled: the remaining solution is dextrorotatory.

Disintegration, page 878—The disintegration time limit for Dextroamphetamine Phosphate Tablets is 15 minutes.

Content uniformity, *Method I,* page 799—Dextroamphetamine Phosphate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed under *Amphetamine Assay,* page 776.

Assay preparation—Weigh and finely powder not less than 20 Dextroamphetamine Phosphate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 6 mg. of dextroamphetamine phosphate, to a 100-ml. beaker, add 2 ml. of hydrochloric acid solution (1 in 100), swirl gently to wet the powder thoroughly, warm on a steam bath for 1 minute, with occasional gentle swirling, and cool. Add 3 g. of purified siliceous earth, and mix until a fluffy mixture is obtained.

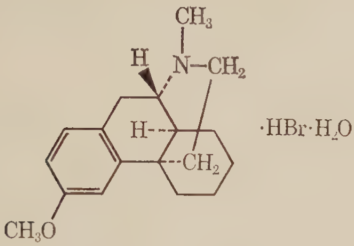
Procedure—Proceed as directed under *Amphetamine Assay,* page 776. Calculate the quantity, in mg., of $C_9H_{13}N.H_3PO_4$ in the portion of the Tablets taken by the formula $0.01C \times 1.266 \times [(A_{U257} - A_{U280})/(A_{S257} - A_{S280})]$, in which C is the exact concentration, in mcg per ml., of USP Dextroamphetamine Sulfate Reference Standard in the *Standard preparation,* and 1.266 is the factor converting dextroamphetamine sulfate to dextroamphetamine phosphate.

Packaging and storage—Preserve Dextroamphetamine Phosphate Tablets in well-closed containers.

Tablets available—Dextroamphetamine Phosphate Tablets usually available contain the following amount of dextroamphetamine phosphate: 5 mg.

Category and Dose—See Dextroamphetamine Phosphate.

Dextromethorphan Hydrobromide*



(+)-3-Methoxy-17-methyl-9α,13α,14α-morphinan Hydrobromide

$C_{18}H_{25}NO.HBr.H_2O$ Mol. wt. 370.33

Dextromethorphan Hydrobromide contains not less than 98.0 percent and not more than 100.5 percent of $C_{18}H_{25}NO.HBr$, calculated on the anhydrous basis.

Description—Dextromethorphan Hydrobromide occurs as practically white crystals, or as a crystalline powder, having a faint odor. It melts at about 126° with decomposition.

Solubility—Dextromethorphan Hydrobromide is sparingly soluble in water. It is freely soluble in alcohol and in chloroform, and is insoluble in ether.

Identification—

A: A solution of Dextromethorphan Hydrobromide (1 in 100) responds to the test for *Bromide*, page 808.

B: To 1 ml. of a solution of ammonium molybdate in sulfuric acid (1 in 100) add about 1 mg. of Dextromethorphan Hydrobromide, and mix: a greenish yellow color develops.

C: Dissolve about 50 mg. of Dextromethorphan Hydrobromide in 2 ml. of diluted sulfuric acid, and add 1 ml. of a freshly prepared solution of mercuric nitrate (dissolve 700 mg. of mercuric nitrate in 4 ml. of water, add 100 mg. of sodium nitrite, mix, and filter): no red color is produced immediately, but after heating, a yellow to red color develops in about 15 minutes.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dextromethorphan Hydrobromide, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Dextromethorphan Hydrobromide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 10,000 solution of Dextromethorphan Hydrobromide exhibits maxima and minima at the same wavelengths as that of NF Dextromethorphan Hydrobromide Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Dextromethorphan Hydrobromide, determined in a solution containing 200 mg. of Dextromethorphan Hydrobromide in each 10 ml. (warming if necessary to obtain complete solution), is between +26° and +28°.

pH, page 824—The pH of a solution of Dextromethorphan Hydrobromide (1 in 100) is between 5.2 and 6.5.

Water, page 900—Determine the water content of Dextromethorphan Hydrobromide by the titrimetric method: not less than 4 percent and not more than 5.5 percent is found.

Residue on ignition, page 858—Dextromethorphan Hydrobromide yields not more than 0.1 percent of residue on ignition.

Dimethylaniline—Transfer to a 25-ml. volumetric flask about 500 mg. of Dextromethorphan Hydrobromide, add 20 ml. of water, and dissolve by warming on a steam bath. Cool, then add 2 ml. of diluted acetic acid and 1 ml. of a solution of sodium nitrite (1 in 100), dilute to volume with water, and mix. This solution shows no more color than corresponds to a solution, similarly prepared, containing 5 mcg. of dimethylaniline in 25 ml. (10 parts per million).

Phenolic compounds—To about 5 mg. of Dextromethorphan Hydrobromide add 1 drop of diluted hydrochloric acid, 1 ml. of water, and 2 drops of ferric chloride T.S. Mix, add 2 drops of potassium ferricyanide T.S., and observe after 2 minutes: no blue-green color develops.

Assay—Dissolve about 700 mg. of Dextromethorphan Hydrobromide, accurately weighed, in a mixture of 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., warming slightly if necessary to effect solution, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 35.23 mg. of $C_{18}H_{25}NO.HBr$.

Packaging and storage—Preserve Dextromethorphan Hydrobromide in tight containers.

CATEGORY—Antitussive.

USUAL DOSE RANGE—**15** to **30 mg.** one to four times a day.

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* Patented. See notice, page ii.

Dextromethorphan Hydrobromide Syrup

Dextromethorphan Hydrobromide Syrup contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{18}H_{25}NO.HBr.H_2O$.

Identification—

A: Transfer about 50 ml. of Dextromethorphan Hydrobromide Syrup to a 250-ml. separator, add 20 ml. of water, 5 ml. of a solution of sodium hydroxide (1 in 10), and 40 ml. of solvent hexane, and shake thoroughly. Remove the solvent hexane layer, and filter it through anhydrous sodium sulfate into a 150-ml. beaker. Repeat the solvent hexane extraction, using two 40-ml. portions, and collecting the extracts in the beaker after filtering. Evaporate the combined extracts to dryness at 50° under nitrogen, then dissolve and dilute the residue in 10 ml. of chloroform: the solution is dextrorotatory. Retain the chloroform solution for *Identification test B*.

B: Evaporate the chloroform solution from *Identification test A* to dryness on a steam bath, dissolve the residue in 2 ml. of diluted sulfuric acid, and proceed as directed in *Identification test C* under *Dextromethorphan Hydrobromide*, page 219.

Reaction—Dextromethorphan Hydrobromide Syrup is acid to litmus.

Assay—Transfer to a 125-ml. separator an accurately measured volume of Dextromethorphan Hydrobromide Syrup, equivalent to about 15 mg. of dextromethorphan hydrobromide, add 20 ml. of water and 3 ml. of 1 N hydrochloric acid, and extract with four 25-ml. portions of solvent hexane, adding a small amount of isopropyl alcohol if an emulsion forms, and discard the solvent hexane extracts. Add 10 ml. of stronger ammonia water to the water layer, and extract the liberated base with three 25-ml. portions of solvent hexane, collecting the extracts in a separator. Wash the combined extracts with two 10-ml. portions of water. Extract the solvent hexane with four 20-ml. portions of 0.1 N hydrochloric acid, collecting the latter in a 100-ml. volumetric flask. Dilute to volume with 0.1 N hydrochloric acid, and mix. Transfer 15.0 ml. of this solution to a 25-ml. volumetric flask, dilute to volume with 0.1 N hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dextromethorphan Hydrobromide Reference Standard in the same medium, at a concentration of about 100 mcg. per ml., in 1-cm. cells, at the maximum at about 278 mμ, with a suitable spectrophotometer, using 0.1 N hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{18}H_{25}NO.HBr.H_2O$, in each ml. of the Syrup taken by the formula $0.167 \times C/V \times (A_U/A_S)$, in which C is the exact concentration of the standard solution, in mcg. per ml., V is the volume, in ml., of the Syrup taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

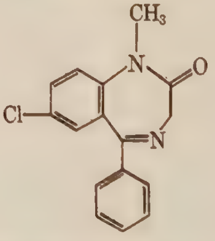
Packaging and storage—Preserve Dextromethorphan Hydrobromide Syrup in tight, light-resistant containers.

Syrup available—Dextromethorphan Hydrobromide Syrup usually available contains the following amount of dextromethorphan hydrobromide: 15 mg. in 5 ml.

Category and Dose—See Dextromethorphan Hydrobromide.

Dextromethorphan Hydrobromide and Terpin Hydrate Elixir, page 686
Dextrose and Sodium Chloride Tablets, page 641
Dextrothyroxine, Sodium, page 646
Dextrothyroxine, Sodium, Tablets, page 647

Diazepam*



7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

$C_{16}H_{13}ClN_2O$ Mol. wt. 284.75

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* Patented. See notice, page ii.

Diazepam contains not less than 98.5 percent and not more than 101.0 percent of $C_{16}H_{13}ClN_2O$, calculated on the dried basis.

Description—Diazepam occurs as an off-white to yellow, practically odorless, crystalline powder.

Solubility—Diazepam is slightly soluble in water and is soluble in alcohol. It is freely soluble in chloroform.

Identification—

A: Prepare a solution of Diazepam in acetone containing 50 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution and 10 μl. of an acetone solution of NF Diazepam Reference Standard containing 50 mg. per ml. Allow the spots to dry, and develop the chromatogram in an unsaturated chamber with a solvent system consisting of ethyl acetate and *n*-heptane (1:1), not saturating the chamber during development, until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with potassium iodoplatinate T.S. The R_f value of the main (purple) spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

B: Dissolve about 5 mg. of Diazepam in 2 ml. of sulfuric acid: the solution shows a green fluorescence under long-wave ultraviolet light.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Diazepam, previously dried in vacuum over phosphorus pentoxide to constant weight, exhibits maxima only at the same wavelengths as that of NF Diazepam Reference Standard, similarly measured.

Ultraviolet absorption, page 866—[NOTE: Use low-actinic glassware.] A 1 in 25,000 solution of Diazepam in 0.1 *N* alcoholic sulfuric acid exhibits an absorbance maximum at 368 ± 2 mμ, and its absorptivity at that maximum is within 2 percent of the absorptivity of a solution of NF Diazepam Reference Standard, similarly measured. A 15 in 50 dilution of the 1 in 25,000 solution in 0.1 *N* alcoholic sulfuric acid exhibits a maximum at 285 ± 2 mμ, and its absorptivity at that maximum is within 3 percent of the absorptivity of a solution of NF Diazepam Reference Standard, similarly measured.

Melting range, page 814—Diazepam melts between 131° and 135°.

Loss on drying, page 814—Dry Diazepam in vacuum over phosphorus pentoxide at 60° to constant weight: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Diazepam yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Diazepam is 20 parts per million.

Assay—Dissolve about 800 mg. of Diazepam, accurately weighed, in 75 ml. of acetic anhydride in a 250-ml. conical flask. Add 5 drops of Nile blue hydrochloride in glacial acetic acid (1 in 100), and titrate the solution with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 28.48 mg. of $C_{16}H_{13}ClN_2O$.

Packaging and storage—Preserve Diazepam in tight, light-resistant containers.

CATEGORY—Tranquilizer (minor).

USUAL DOSE RANGE—Oral, **2** to **10 mg.** two to four times a day. Intramuscular or intravenous, **2** to **10 mg.,** repeated in 3 to 4 hours, if necessary, but no more than 30 mg. should be given in an 8-hour period.

Diazepam Injection

Diazepam Injection is a sterile solution of diazepam in water for injection or other suitable medium. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{13}ClN_2O$.

Identification—

A: The solution prepared for measurement of absorbance in the *Assay* exhibits a maximum at 368 ± 2 mμ. A 15 in 50 ml. dilution of this solution in 0.1 *N* alcoholic sulfuric acid exhibits a maximum at 285 ± 2 mμ.

B: Using 30 μl. of Diazepam Injection as the sample solution and 10 μl. of a solution of NF Diazepam Reference Standard in acetone containing 15 mg. per ml. as the standard solution, and ethyl acetate as the solvent, proceed as directed for *Identification Test A* under *Diazepam*, page 220.

pH, page 824—The pH of Diazepam Injection is between 6.2 and 6.9.

Other requirements—Diazepam Injection meets the requirements under *Injections*, page 810.

Assay—Transfer to a suitable separator an accurately measured volume of

Diazepam Injection, equivalent to about 10 mg. of diazepam. Add 20 ml. of pH 7 buffer solution (prepared by mixing 104.5 ml. of 0.2 *M* dibasic sodium phosphate and 85.5 ml. of 0.2 *M* monobasic potassium phosphate in a 1000-ml. volumetric flask, diluting to volume with water, and adjusting the pH, if necessary, to 7.0), and extract with four 20-ml. portions of chloroform, passing each extract through about 5 g. of anhydrous sodium sulfate and combining the extracts in a 100-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 10.0 ml. of this solution into a 25-ml. volumetric flask, evaporate the chloroform under nitrogen, add 0.1 *N* alcoholic sulfuric acid to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Diazepam Reference Standard in 0.1 *N* alcoholic sulfuric acid at a concentration of about 40 mcg. per ml., in 1-cm. cells, at the maximum at about 368 mμ, with a suitable spectrophotometer, using 0.1 *N* alcoholic sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{13}ClN_2O$ in each ml. of the Injection taken by the formula $0.25 \times (C/V) \times (A_U/A_S)$, in which *C* is the exact concentration, in mcg. per ml., of the Reference Standard solution, and *V* is the volume, in ml., of the Injection taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Diazepam Injection in single-dose or multiple-dose containers, preferably of Type I glass, protected from light.

Injection available—Diazepam Injection usually available contains the following amount of diazepam: 10 mg. in 2 ml.

CATEGORY and DOSE—See Diazepam.

Diazepam Tablets

Diazepam Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{13}ClN_2O$.

Identification—

A: The solution prepared for measurement of absorbance in the *Assay* exhibits maxima at 368 ± 2 mμ and at 285 ± 2 mμ.

B: Shake a portion of finely powdered Diazepam Tablets, equivalent to about 10 mg. of diazepam, with 10 ml. of acetone, filter, evaporate the filtrate to dryness under nitrogen, and dissolve the residue in 2 ml. of sulfuric acid: the solution shows a green fluorescence under long-wave ultraviolet light.

Disintegration, page 878—The disintegration time limit for Diazepam Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—[NOTE: Use low-actinic glassware.] Diazepam Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Place one tablet in an appropriate container and add 5 ml. of water. Let stand for about 20 to 30 minutes to allow the tablet to disintegrate, then add 5 ml. of methanol, and mix. Dilute this solution quantitatively and stepwise, if necessary, with 0.1 *N* alcoholic sulfuric acid to provide a solution containing approximately 10 mcg. of diazepam per ml., and filter. Concomitantly determine the absorbance of this solution and of a solution of NF Diazepam Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 285 mμ, with a suitable spectrophotometer, using 0.1 *N* alcoholic sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{13}ClN_2O$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which *T* is the labeled quantity of diazepam, in mg., in the tablet; *D* is the exact concentration, in mcg. per ml., of diazepam in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; *C* is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—[*Note:* Use low-actinic glassware.] Weigh and finely powder not less than 20 Diazepam Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 4 mg. of diazepam, to a glass-stoppered centrifuge tube, and add 40 ml. of chloroform. Shake the mixture mechanically for 20 minutes, and then centrifuge. Transfer the chloroform extract to a 100-ml. volumetric flask. Repeat the extraction procedure with a 30-ml. portion of chloroform, then with a 20-ml. portion of chloroform, combining the extracts in the volumetric flask, and dilute to volume with chloroform. Transfer this solution to a 250-ml. separator, and add 40 ml. of pH 9.7 borate buffer solution (prepared by mixing 30 ml. of 0.1 *N* sodium hydroxide with 70 ml. of a solution made with 12.4 g. of boric acid dissolved in 100 ml. of 1 *N* sodium hydroxide and diluted to 1000 ml. with water). Shake well, and pass the chloroform layer through a funnel containing a pledget of glass wool layered with 1 g. of anhydrous sodium sulfate.

Pipet 10.0 ml. of the filtrate into a 50-ml. volumetric flask, and evaporate to dryness under a stream of nitrogen. Using 0.1 *N* alcoholic sulfuric acid, dissolve the residue, then dilute to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Diazepam Reference Standard, in the same medium, at a concentration of about 8 mcg. per ml., in 1-cm. cells, at the maximum at about 285 mμ, with a suitable spectrophotometer, using 0.1 *N* alcoholic sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{13}ClN_2O$ in the portion of the Tablets taken, by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

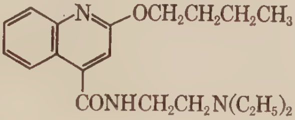
Packaging and storage—Preserve Diazepam Tablets in tight, light-resistant containers.

Tablets available—Diazepam Tablets usually available contain the following amounts of diazepam: 2, 5, and 10 mg.

CATEGORY and DOSE—See Diazepam.

Dibasic Calcium Phosphate, page 125

Dibucaine



2-Butoxy-*N*-[2-(diethylamino)ethyl]cinchoninamide

$C_{20}H_{29}N_3O_2$ Mol. wt. 343.47

Dibucaine contains not less than 97.0 percent and not more than 100.5 percent of $C_{20}H_{29}N_3O_2$, calculated on the dried basis.

Description—Dibucaine occurs as a colorless or almost colorless powder. It is odorless, is somewhat hygroscopic, and darkens on exposure to light.

Solubility—Dibucaine is soluble in 1 *N* hydrochloric acid and in ether. It is slightly soluble in water.

Melting range, page 814—Dibucaine, previously dried over phosphorus pentoxide overnight, melts between 62° and 65°.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Dibucaine in 1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of USP Dibucaine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis in terms of the base, at the point of maximum absorbance occurring at about 247 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Dibucaine over phosphorus pentoxide overnight: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 250 mg. of Dibucaine is negligible.

Assay—Dissolve about 300 mg. of Dibucaine, accurately weighed, in 50 ml. of glacial acetic acid, warming slightly if necessary to effect solution. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 17.17 mg. of $C_{20}H_{29}N_3O_2$.

Packaging and storage—Preserve Dibucaine in tight, light-resistant containers.

CATEGORY—Local anesthetic.

APPLICATION—Topically as a 0.5 percent cream or a 1 percent ointment several times a day.

Dibucaine Cream

Dibucaine Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{29}N_3O_2$ in a suitable cream base.

Identification—The ultraviolet absorption spectrum of the solution employed for the measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of the solution of USP Dibucaine Hydrochloride Reference Standard prepared as directed in the *Assay*.

Weight variation, page 901—Dibucaine Cream meets the requirements of the weight variation test for creams.

Assay—Accurately weigh a portion of Dibucaine Cream, equivalent to about 10 mg. of dibucaine, into a glass-stoppered 125-ml. conical flask. Add 25 ml. of 1 *N* hydrochloric acid, heat on a steam bath to melt the sample, and then shake vigorously. Cool under running water and filter through paper by decanting into a separator, retaining as much as possible of the congealed portion from the sample in the flask. Repeat the extraction with two additional 25-ml. portions of 1 *N* hydrochloric acid, filtering each portion into the separator. Slowly add 10 ml. of 10 *N* sodium hydroxide, cool, and extract the alkaline solution with three 25-ml. portions of ether, combining the ether extracts in another separator. Extract the ether solution with three 25-ml. portions of 1 *N* hydrochloric acid, filtering the extracts into a 100-ml. volumetric flask. Rinse the filter paper with 10 ml. of 1 *N* hydrochloric acid, dilute to volume with 1 *N* hydrochloric acid, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of USP Dibucaine Hydrochloride Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at a maximum of about 247 mμ, with a suitable spectrophotometer, using 1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{20}H_{29}N_3O_2$ in the portion of Cream taken by the formula $C \times 0.9040 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, 0.9040 is the factor converting dibucaine hydrochloride to dibucaine, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Dibucaine Cream in collapsible tubes or in tight containers.

Cream available—Dibucaine Cream usually available contains 0.5 percent of dibucaine.

Category and Application—See Dibucaine.

Dibucaine Ointment

Dibucaine Ointment contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{29}N_3O_2$ in a suitable ointment base.

Identification—The ultraviolet absorption spectrum of the solution employed for the measurement of absorbance in the *Assay* exhibits maxima and minima only at the same wavelengths as that of the solution of USP Dibucaine Hydrochloride Reference Standard prepared as directed in the *Assay*.

Weight variation, page 901—Dibucaine Ointment meets the requirements of the weight variation test for ointments.

Assay—Weigh accurately a portion of Dibucaine Ointment, equivalent to about 10 mg. of dibucaine, transfer to a separator containing 50 ml. of ether, and mix to dissolve. Extract successively with three 25-ml. portions and one 10-ml. portion of 1 *N* hydrochloric acid, filtering the extracts into another separator. Continue as directed in the *Assay* under *Dibucaine Cream*, page 223, beginning with "Slowly add 10 ml. of 10 *N* sodium hydroxide. . . ." Calculate the quantity, in mg., of $C_{20}H_{29}N_3O_2$ in the portion of Ointment taken by the formula $C \times 0.9040 \times (A_U/A_S)$.

Packaging and storage—Preserve Dibucaine Ointment in collapsible tubes or in tight containers.

Ointment available—Dibucaine Ointment usually available contains 1 percent of dibucaine.

Category and Application—See Dibucaine.

Dichlorodifluoromethane

CCl_2F_2

CCl_2F_2 Mol. wt. 120.91

Description — Dichlorodifluoromethane occurs as a clear, colorless gas having a faint, ethereal odor. Its vapor pressure at 25° is about 4883 mm. of mercury (80 psig).

Identification—The infrared absorption spectrum of Dichlorodifluoromethane, determined in a 10-cm. cell with sodium chloride windows, at atmospheric pressure, exhibits maxima, among others, at the following wavelengths, in μ: 4.33 (*m*), 4.46 (*m*), 4.56 (*m*), 6.29 (*m*), 7.25 (*m*), 8.05 (*s*), 8.63 (*s*), 9.1 (*vs*), 10.7 (*vs*), 10.8 (*vs*), 11.2 (*m*), 11.3 (*m*), 13.1 (*w*), and 13.9 (*w*). The stronger maxima are best obtained at pressures less than 10 mm. of mercury.

Boiling temperature—Determine the boiling temperature of Dichlorodifluoromethane by the special procedure, page 782: it boils at approximately −30°.

Water—Determine the water content of Dichlorodifluoromethane by the special procedure, page 900: not more than 10 parts per million is found.

High-boiling residues—Determine the content of high-boiling residues in Dichlorodifluoromethane by the special procedure, page 772: not more than 0.01 percent is found.

Inorganic chlorides—Place 5 ml. of dehydrated methanol in a test tube, add 3 drops of a saturated solution of silver nitrate in dehydrated methanol, shake, and add 7 g. of Dichlorodifluoromethane: no opalescence or turbidity is produced.

Packaging and storage—Preserve Dichlorodifluoromethane in tight cylinders, in a cool place.

CATEGORY—Aerosol propellant.

Dichlorotetrafluoroethane

$CClF_2$-$CClF_2$

1,2-Dichlorotetrafluoroethane

$C_2Cl_2F_4$ Mol. wt. 170.92

Description—Dichlorotetrafluoroethane occurs as a clear, colorless gas having a faint, ethereal odor. Its vapor pressure at 25° is about 1621 mm. of mercury (17 psig). It usually contains from 6 to 10 percent of its isomer, CCl_2F-CF_3.

Identification—The infrared absorption spectrum of Dichlorotetrafluoroethane, determined in a 10-cm. cell with sodium chloride windows, at atmospheric pressure, exhibits maxima, among others, at the following wavelengths, in μ: 4.34 (*s*), 4.48 (*m*), 5.28 (*m*), 5.95 (*m*), 7.36 (*s*), 9.5 (*vs*), 10.9 (*vs*), 11.8 (*vs*), 13.6 (*s*), and 14.8 (*s*). The stronger maxima are best obtained at pressures less than 10 mm. of mercury.

Boiling temperature—Determine the boiling temperature of Dichlorotetrafluoroethane by the special procedure, page 772: it boils at approximately 4°.

Water—Determine the water content of Dichlorotetrafluoroethane by the special procedure, page 772: not more than 10 parts per million is found.

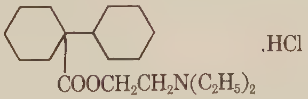
High-boiling residues—Determine the content of high-boiling residues in Dichlorotetrafluoroethane by the special procedure, page 772: not more than 0.01 percent is found.

Inorganic chlorides—Place 5 ml. of dehydrated methanol in a test tube, add 3 drops of a saturated solution of silver nitrate in dehydrated methanol, shake, and add 7 g. of Dichlorotetrafluoroethane: no opalescence or turbidity is produced.

Packaging and storage—Preserve Dichlorotetrafluoroethane in tight cylinders, in a cool place.

CATEGORY—Aerosol propellant.

Dicyclomine Hydrochloride



2-(Diethylamino)ethyl [Bicyclohexyl]-1-carboxylate Hydrochloride

$C_{19}H_{35}NO_2 \cdot HCl$ Mol. wt. 345.96

Dicyclomine Hydrochloride contains not less than 99.0 percent and not more than 102.0 percent of $C_{19}H_{35}NO_2 \cdot HCl$, calculated on the dried basis.

Description—Dicyclomine Hydrochloride occurs as a fine, white, crystalline powder. It is practically odorless and has a very bitter taste.

Solubility—Dicyclomine Hydrochloride is soluble in water, freely soluble in alcohol and in chloroform, and very slightly soluble in ether.

Melting range, page 814—Dicyclomine Hydrochloride melts between 169° and 174°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dicyclomine Hydrochloride, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Dicyclomine Hydrochloride Reference Standard, similarly measured.

Loss on drying, page 814—Dry Dicyclomine Hydrochloride at 105° for 4 hours: it loses not more than 1 percent of its weight.

pH, page 824—The pH of a solution of Dicyclomine Hydrochloride (1 in 100) is between 5.0 and 5.5.

Readily carbonizable substances, page 856—Dissolve 500 mg. of Dicyclomine Hydrochloride in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid D.

Assay—Dissolve about 600 mg. of Dicyclomine Hydrochloride, accurately weighed, in 70 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 N perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N perchloric acid is equivalent to 34.60 mg. of $C_{19}H_{35}NO_2.HCl$.

Packaging and storage—Preserve Dicyclomine Hydrochloride in well-closed containers.

CATEGORY—Anticholinergic.

USUAL DOSE RANGE—**10** to **20 mg.** three or four times a day.

Dicyclomine Hydrochloride Capsules

Dicyclomine Hydrochloride Capsules contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{19}H_{35}NO_2.HCl$.

Identification—

A: Mix a quantity of the contents of Dicyclomine Hydrochloride Capsules, equivalent to about 10 mg. of dicyclomine hydrochloride, with 5 ml. of water, and 2 ml. of diluted nitric acid, filter, and to the filtrate add 2 ml. of silver nitrate T.S.: a white precipitate is produced.

B: Mix gently in a cylinder 3 ml. of sodium lauryl sulfate solution (1 in 1000) with 10 ml. of chloroform and 0.2 ml. of methylene blue T.S., and allow the layers to separate. Transfer to the cylinder a quantity of the contents of Dicyclomine Hydrochloride Capsules, equivalent to about 20 mg. of dicyclomine hydrochloride, dissolved in 5 ml. of water, mix gently, allow the phases to separate and allow to stand for 30 minutes: the blue color migrates from the chloroform phase to the aqueous phase.

Content uniformity, *Method I,* page 798—Dicyclomine Hydrochloride Capsules meet the requirements of the content uniformity test for capsules.

Assay—

Sodium lauryl sulfate, 0.004 M—Dissolve 1.15 g. of sodium lauryl sulfate in about 500 ml. of water, dilute to 1000.0 ml. with water, and mix. Determine the molarity of the solution as follows: transfer to a glass-stoppered cylinder 10.0 ml. of a 0.004 M solution of NF Dicyclomine Hydrochloride Reference Standard (1.384 mg. of $C_{19}H_{35}NO_2.HCl$ per ml.), add 5 ml. of diluted sulfuric acid, 20 ml. of chloroform, and 1 ml. of alcoholic methyl yellow solution (1 in 10,000), and titrate with the sodium lauryl sulfate solution, with frequent shaking, until the chloroform layer acquires a permanent orange-pink color. Calculate the molarity, and restandardize before each use.

Procedure—Transfer as completely as possible the contents of not less than 20 Dicyclomine Hydrochloride Capsules to a suitable tared container, determine the average content weight per capsule, and mix the combined contents thoroughly. Transfer an accurately weighed portion, equivalent to about 20 mg. of dicyclomine hydrochloride, to a 100-ml. glass-stoppered cylinder, and add 20 ml. of water, 5 ml. of diluted sulfuric acid, 20 ml. of chloroform, and 1 ml. of alcoholic methyl yellow solution (1 in 10,000). Stopper the cylinder, shake until the chloroform phase develops a bright yellow color, and titrate with 0.004 M sodium lauryl sulfate, shaking thoroughly after each addition, until the chloroform develops the first orange-pink color. Each ml. of 0.004 M sodium lauryl sulfate is equivalent to 1.384 mg. of $C_{19}H_{35}NO_2.HCl$.

Packaging and storage—Preserve Dicyclomine Hydrochloride Capsules in tight containers.

Capsules available—Dicyclomine Hydrochloride Capsules usually available contain the following amount of dicyclomine hydrochloride: 10 mg.

CATEGORY and DOSE—See Dicyclomine Hydrochloride.

Dicyclomine Hydrochloride Syrup

Dicyclomine Hydrochloride Syrup contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{19}H_{35}NO_2.HCl$.

Identification—

A: To a volume of Dicyclomine Hydrochloride Syrup, equivalent to about 10 mg. of dicyclomine hydrochloride, add 0.2 ml. of diluted nitric acid and 2 ml. of silver nitrate T.S.: a white precipitate is produced.

B: Mix gently in a cylinder 3 ml. of sodium lauryl sulfate solution (1 in 1000) with 10 ml. of chloroform and 0.2 ml. of methylene blue T.S. Allow the phases to separate, then add a volume of Dicyclomine Hydrochloride Syrup, equivalent to about 20 mg. of dicyclomine hydrochloride, mix gently, allow the phases to separate, and allow to stand for 30 minutes: the blue color migrates from the chloroform phase to the aqueous phase.

Assay—

Sodium lauryl sulfate, 0.004 M—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*, page 226.

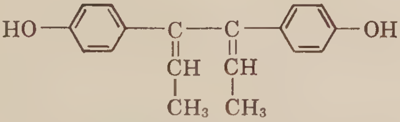
Procedure—Transfer an accurately measured volume of Dicyclomine Hydrochloride Syrup, equivalent to about 20 mg. of dicyclomine hydrochloride, to a 100-ml. glass-stoppered cylinder, add 5 ml. of diluted sulfuric acid and 2 ml. of 0.1 *N* potassium permanganate solution, and mix. When the solution becomes colorless, add 20 ml. of water, 20 ml. of chloroform, and 1 ml. of alcoholic methyl yellow solution (1 in 10,000). Stopper the cylinder, shake until the chloroform phase develops a bright yellow color, and then titrate with 0.004 *M* sodium lauryl sulfate, shaking thoroughly after each addition, until the chloroform develops the first orange-pink color. Each ml. of 0.004 *M* sodium lauryl sulfate is equivalent to 1.384 mg. of $C_{19}H_{35}NO_2.HCl$.

Packaging and storage—Preserve Dicyclomine Hydrochloride Syrup in tight containers.

Syrup available—Dicyclomine Hydrochloride Syrup usually available contains the following amount of dicyclomine hydrochloride: 10 mg. in 5 ml.

CATEGORY and DOSE—See Dicyclomine Hydrochloride.

Dienestrol



4,4′-(Diethylideneethylene)diphenol

$C_{18}H_{18}O_2$ Mol. wt. 266.34

Dienestrol contains not less than 98.0 percent and not more than 100.5 percent of $C_{18}H_{18}O_2$, calculated on the dried basis.

Description—Dienestrol occurs as colorless or white, or practically white, needle-like crystals or as a white, or practically white, crystalline powder. It is odorless.

Solubility—Dienestrol is practically insoluble in water. It is soluble in alcohol, in acetone, in ether, in methanol, in propylene glycol, and in solutions of alkali hydroxides. It is slightly soluble in chloroform, and in fatty oils.

Identification—

A: The diacetate obtained in the *Assay* melts between 118° and 125°, page 814.

B: To a solution of about 10 mg. of Dienestrol in 0.5 ml. of alcohol add 1 ml. of hydrochloric acid and about 50 mg. of vanillin: a blue color is produced immediately, and it persists on dilution with water but disappears on the addition of alkali (*diethylstilbestrol* produces no color).

Melting range, *Class Ia*, page 815—Dienestrol melts within a range of 3° between 227° and 234°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dienestrol, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Dienestrol Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Dienestrol in alcohol exhibits maxima and minima at the same wavelengths as that of NF Dienestrol

Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 228 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Dienestrol at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Dienestrol yields not more than 0.15 percent of residue on ignition.

Assay—Weigh accurately about 500 mg. of Dienestrol, add 2 ml. of acetic anhydride and 4 ml. of pyridine, and reflux for 15 minutes. Cool, add 50 ml. of water, shake vigorously, and allow to stand in a stoppered flask in a refrigerator overnight. Collect the precipitate on a tared filter crucible, wash it with water until the odor of pyridine is no longer perceptible, and dry in vacuum at room temperature for 5 hours. The weight of the diacetate so obtained, multiplied by 0.7601, represents its equivalent of $C_{18}H_{18}O_2$.

Packaging and storage—Preserve Dienestrol in tight, light-resistant containers.

CATEGORY—Estrogen.

USUAL DOSE—**500 mcg.** daily.

USUAL DOSE RANGE—**100 mcg.** to **1.5 mg.**

APPLICATION—Vaginal, **5 g.** of a 0.01 percent cream once or twice a day for 7 to 14 days, then once every 48 hours for 7 to 14 days.

Dienestrol Cream

Dienestrol Cream is dienestrol in a suitable water-miscible base. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{18}H_{18}O_2$.

Identification—The polarogram of the *Assay preparation* employed for measurement in the *Assay* exhibits a half-wave potential ($E_{1/2}$) within 1 percent of that of the *Standard preparation,* similarly measured.

Weight variation, page 901—Dienestrol Cream meets the requirements of the weight variation test for creams.

Assay—

pH 6.5 Phosphate buffer—Dissolve 315.2 mg. of monobasic potassium phosphate in 20 ml. of water, add 12.0 ml. of 0.1 *N* sodium hydroxide, dilute to 100.0 ml. with water, and mix. Adjust the pH to 6.5 with 0.1 *N* hydrochloric acid.

Electrolyte solution—Transfer 5.4 g. of ammonium chloride and 45 ml. of stronger ammonia water to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Chromatographic column—Pack a pledget of glass wool in the base of a 20 × 1.5-cm. (outside diameter) chromatographic tube. Nearly fill the tube with a 1:1 mixture of ether and *n*-hexane, and then slowly pour into the tube a slurry of 5 g. of chromatographic silica gel (60/80 mesh) in 10 ml. of ether–*n*-hexane mixture. Open the stopcock, allow the silica gel to settle by gravity, and tamp into a uniform column bed. Allow at least 5 ml. head of solvent mixture to remain on the column until ready for use, and then allow the meniscus to descend to the top of the bed.

Standard preparation—Dissolve in methanol a suitable quantity of NF Dienestrol Reference Standard, accurately weighed, and then dilute, quantitatively and stepwise with methanol to obtain a solution of known concentration, containing about 50 mcg. per ml. Pipet 2.0 ml. of this solution into a glass-stoppered test tube, and evaporate to dryness under reduced pressure. Continue as directed under *Assay preparation,* beginning with "Dissolve the residue in 5.0 ml. of dilute acetic acid (8 in 10). . . ."

Assay preparation—Transfer to a 30-ml. glass-stoppered test tube an accurately weighed quantity, in duplicate, of Dienestrol Cream, equivalent to about 100 mcg. of dienestrol. Add 5.0 ml. of *pH 6.5 Phosphate buffer* and 15 ml. of ether, and shake for 2 minutes. Transfer the ether layer to a second glass-stoppered test tube. Extract the aqueous layer with two 10-ml. portions of ether, adding the extracts to the second tube. Evaporate the combined ether extracts to dryness under reduced pressure, add 10 ml. of dehydrated alcohol,† stopper loosely, and heat in a water bath maintained at 80° until a clear solution forms. Add 1.3 g. of urea, and continue heating, with shaking, until dissolved. Allow to stand at room temperature for about 2 hours, add 5 ml. of a 1:1 mixture of ether and *n*-hexane, and then chill in a refrigerator (4°) for 30 minutes. Immediately centrifuge, and decant the supernatant liquid into a 30-ml. glass-stoppered test tube. Wash the precipitate with two 5-ml. portions of a 1:1 mixture of ether and *n*-hexane, centrifuging after each washing. Combine all of the washings,† and evaporate under reduced pressure to a volume of about 1 ml. Quantitatively transfer this residual mixture to the chromatographic column, with the aid of about 5 ml. of the ether-*n*-hexane mixture, and open the stopcock on the column, allowing the sample to enter the column bed. Wash the sides of the column with the ether–*n*-hexane mixture, and elute the column with 75 ml. of this solvent, collecting the eluate in a 150-ml. beaker. Evaporate the residue to dryness in small portions in a glass-stoppered test tube under reduced pressure.

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† At this point the procedure may be stopped overnight.

Dissolve the residue in 5.0 ml. of dilute acetic acid (8 in 10), prepared by diluting 80 ml. of glacial acetic acid to 100 ml. with water, and carefully pipet 4.0 ml. of this solution into a 25-ml. volumetric flask. To the flask add 3 drops of sulfuric acid and 5 drops of a freshly prepared saturated solution of sodium nitrite, allow the reaction to proceed for 30 minutes, and then immerse the flask in an ice bath. Add 20 ml. of *Electrolyte solution*, allow the fuming to subside, then remove the flask from the ice bath, dilute to volume with *Electrolyte solution*, and mix. Allow this solution to stand for at least 30 minutes but not longer than 2 hours before using as directed in the *Procedure*.

Procedure—Filter a portion of the *Assay preparation* through a pledget of cotton into a polarographic cell, and deaerate by bubbling nitrogen through the solution for at least 10 minutes. Insert the dropping electrode of a suitable polarograph, and record the polarogram from -0.25 volt to -1.25 volts. Determine the height of the diffusion current $[(i_d)_U]$ between -0.45 volt and -0.95 volt, *versus* a saturated calomel reference electrode, and correct for solution blank. Concomitantly and similarly determine the diffusion current $[(i_d)_S]$ of the *Standard preparation*. Calculate the quantity, in mcg., of $C_{18}H_{18}O_2$ in the portion of Cream taken by the formula $31.25C \times [(i_d)_U/(i_d)_S]$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Dienestrol Cream in tight containers.

Cream available—Dienestrol Cream usually available contains 0.01 percent of dienestrol.

CATEGORY and APPLICATION—See Dienestrol.

Dienestrol Tablets

Dienestrol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{18}H_{18}O_2$.

Identification—

A: Pulverize a suitable number of Dienestrol Tablets, and extract the powder with several portions of ether. Allow the ether to evaporate, and dry the residue at about 80° for 1 hour: the residue so obtained responds to *Identification test B* under *Dienestrol*, page 227, and after recrystallization from alcohol melts between 227° and 234°, page 814.

B: The polarogram of the *Assay preparation* employed for measurement in the *Assay* exhibits a half-wave potential ($E_{1/2}$) within 1 percent of that of the *Standard preparation* similarly measured.

Disintegration, page 878—The disintegration time limit for Dienestrol Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Dienestrol Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Buffer solution—Transfer 1.5 g. of potassium hydroxide to a 100-ml. volumetric flask, add 10 ml. of water to dissolve, add 80 ml. of glacial acetic acid, dilute to volume, and mix.

Electrolyte solution—Transfer 5.4 g. of ammonium chloride and 45 ml. of stronger ammonia water to a 100-ml. volumetric flask, dilute to volume, and mix.

Standard preparation—Dissolve a suitable quantity, accurately weighed, of NF Dienestrol Reference Standard in methanol, and then dilute, quantitatively and stepwise, with methanol to obtain a solution of known concentration, containing about 50 mcg. per ml. Pipet 2.0 ml. of this solution into a glass-stoppered test tube, and evaporate to dryness under reduced pressure. Continue as directed under *Assay preparation*, beginning with "Dissolve the residue in 5.0 ml. of *Buffer solution*. . . ."

Assay preparation—Pack a pledget of fine glass wool in the base of a 20 × 1.5 cm. (outside diameter) chromatographic tube. Intimately mix 500 mg. of acid-washed chromatographic siliceous earth with 1.0 ml. of 1 *N* tribasic sodium phosphate, transfer the mixture to the tube, and pack gently with a tamping rod.

Weigh and finely powder not less than 20 Dienestrol Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mcg. of dienestrol, to a 50-ml. beaker, add 1.0 ml. of 1 *N* tribasic sodium phosphate and 1 g. of acid-washed chromatographic siliceous earth, and mix until the mixture is fluffy. Transfer the mixture quantitatively to the column, and pack gently to a uniform mass with a tamping rod. Place a pledget of glass wool on the top of the column. Wash the column with 80 ml. of *n*-hexane, and discard the eluate. Elute the dienestrol from the column with 150 ml. of water-washed chloroform, and evaporate the eluate to dryness on a steam bath with the aid of a current of air. Dissolve the residue in 5.0 ml. of *Buffer solution*, and carefully pipet 4.0 ml. of this solution into a 25-ml. volumetric flask. To the flask add 3 drops of sulfuric acid and 5 drops of a freshly prepared saturated solution of sodium nitrite, allow the reaction to proceed for 30 minutes, and then immerse the flask in an ice bath. Add 20 ml. of *Electrolyte solution*, allow the fuming to subside, then remove the flask from the ice bath, dilute to volume with *Electrolyte solution*, and mix. Allow this solution to stand for at least 30 minutes but not longer than 2 hours before using as directed in the *Procedure*.

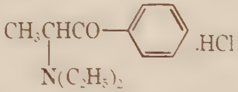
Procedure—Filter a portion of the *Assay preparation* through a pledget of cotton into a polarographic cell, and de-aerate by bubbling nitrogen through the solution for at least 10 minutes. Insert the dropping electrode of a suitable polarograph, and record the polarogram from −0.25 volt to −1.25 volts. Determine the height of the diffusion current $[(i_d)_U]$ between −0.45 volt and −0.95 volt, *versus* a saturated calomel reference electrode, and correct for solution blank. Concomitantly and similarly determine the diffusion current $[(i_d)_S]$ of the *Standard preparation*. Calculate the quantity, in mcg., of $C_{18}H_{18}O_2$ in the portion of Tablets taken by the formula $31.25C \times [(i_d)_U/(i_d)_S]$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Dienestrol Tablets in well-closed containers.

Tablets available—Dienestrol Tablets usually available contain the following amounts of dienestrol: 100 mcg. and 500 mcg.

Category and Dose—See Dienestrol.

Diethylpropion Hydrochloride*



2-(Diethylamino)propiophenone Hydrochloride

$C_{13}H_{19}NO.HCl$ Mol. wt. 241.76

Diethylpropion Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{13}H_{19}NO.HCl$, calculated on the anhydrous basis.

Description—Diethylpropion Hydrochloride occurs as a white to off-white, fine crystalline powder. It has a slight characteristic odor. It melts at about 175° with decomposition.

Solubility—Diethylpropion Hydrochloride is freely soluble in water, in chloroform, and in alcohol. It is practically insoluble in ether.

Identification—

A: A solution of Diethylpropion Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 808.

B: Dissolve about 25 mg. of Diethylpropion Hydrochloride in 2 ml. of a solution containing 2 g. of citric acid (monohydrate) in 100 ml. of acetic anhydride and heat for about 15 minutes on a steam bath: a red to purple color develops.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Diethylpropion Hydrochloride, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Diethylpropion Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Diethylpropion Hydrochloride in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Diethylpropion Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance occurring at about 253 $m\mu$, do not differ by more than 3 percent.

Water, page 900—Determine the water content of Diethylpropion Hydrochloride by the titrimetric method: not more than 1 percent is found.

Secondary amines—Dissolve about 5 mg. of Diethylpropion Hydrochloride in a few drops of water on a spot plate. Add, in succession, 1 drop of sodium carbonate solution (1 in 5), 2 drops of acetaldehyde T.S., and 1 drop of sodium nitroferricyanide solution (1 in 100): a reddish color may develop within 3 to 5 minutes, but no dark blue color appears.

Free bromine—One drop of a 1 in 10 solution of Diethylpropion Hydrochloride produces no discoloration when placed upon starch iodide paper.

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* Patented. See notice, page ii.

Hydrobromic acid and bromide—To 10 ml. of a solution of Diethylpropion Hydrochloride (1 in 10) add 2 drops of diluted hydrochloric acid, 0.5 ml. of chloroform, 0.5 ml. of freshly prepared Chloramine-T solution (1 in 10), and shake vigorously: no yellow or brown-red color is formed in the chloroform layer.

Assay—Transfer about 250 mg. of Diethylpropion Hydrochloride, accurately weighed, to a 500-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Pipet 5.0 ml. of this solution into a 250-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Diethylpropion Hydrochloride Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 253 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{13}H_{19}NO.HCl$ in the Diethylpropion Hydrochloride taken by the formula $25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Diethylpropion Hydrochloride in well-closed containers, protected from light.

CATEGORY—Anorexic.

USUAL DOSE—**25 mg.** three times a day.

Diethylpropion Hydrochloride Tablets

Diethylpropion Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{13}H_{19}NO.HCl$.

Identification—

A: A portion of finely powdered Diethylpropion Hydrochloride Tablets, equivalent to about 25 mg. of diethylpropion hydrochloride, responds to *Identification test B* under *Diethylpropion Hydrochloride,* page 230.

B: The ultraviolet absorption spectrum of the solution prepared from Diethylpropion Hydrochloride Tablets for measurement of absorption in the *Assay* exhibits maxima and minima at the same wavelengths as that of the Reference Standard solution, similarly measured.

Disintegration, page 878—The disintegration time limit for Diethylpropion Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Diethylpropion Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask containing about 65 ml. of 0.1 *N* hydrochloric acid. Shake frequently during a 10-minute period, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Allow the insoluble material to settle, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate, quantitatively and stepwise, if necessary, with 0.1 *N* hydrochloric acid, to provide a solution containing approximately 10 mcg. of diethylpropion hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Diethylpropion Hydrochloride Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 253 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{13}H_{19}NO.HCl$, in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of diethylpropion hydrochloride in the tablet; D is the exact concentration, in mcg. per ml., of diethylpropion hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

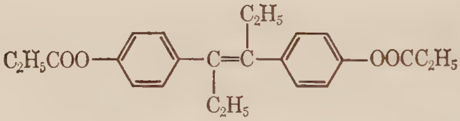
Assay—Weigh and finely powder not less than 20 Diethylpropion Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg. of diethylpropion hydrochloride, to a 25-ml. glass-stoppered cylinder containing about 25 ml. of 0.1 *N* hydrochloric acid. Shake at intervals over a 10-minute period. Filter this solution through a suitable wetted filter paper into a 125-ml. separator, and wash the cylinder and filter paper with three 10-ml. portions of 0.1 *N* hydrochloric acid, adding the washes to the separator. Add 5 ml. of sodium hydroxide solution (1 in 10) to the separator, mix, and extract with three 50-ml. portions of chloroform. Extract the combined chloroform extracts with three 50-ml. portions of 0.1 *N* hydrochloric acid, collecting the extracts in a 250-ml. volumetric flask. Dilute to volume with 0.1 *N* hydrochloric acid, and mix. Pipet 25.0 ml. of this solution into a 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Diethylpropion Hydrochloride Reference Standard, in 0.1 *N* hydrochloric acid at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 253 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{13}H_{19}NO.HCl$ in the portion of the Tablets taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Diethylpropion Hydrochloride Tablets in well-closed containers.

Tablets available—Diethylpropion Hydrochloride Tablets usually available contain the following amount of diethylpropion hydrochloride: 25 mg.

CATEGORY and DOSE—See Diethylpropion Hydrochloride.

Diethylstilbestrol Dipropionate



(*E*)-α,α'-Diethyl-4,4′-stilbenediol Dipropionate

$C_{24}H_{28}O_4$ Mol. wt. 380.49

Diethylstilbestrol Dipropionate contains not less than 98.0 percent and not more than 100.5 percent of $C_{24}H_{28}O_4$, calculated on the dried basis.

Description—Diethylstilbestrol Dipropionate occurs as a white, odorless, tasteless, crystalline powder. A suspension of Diethylstilbestrol Dipropionate in diluted alcohol (1 in 100) is neutral to litmus paper.

Solubility—Diethylstilbestrol Dipropionate is very slightly soluble in water and in dilute mineral acids. It is insoluble in solutions of alkali hydroxides. It is soluble in vegetable oils, and is freely soluble in acetone, in benzene, in chloroform, in ether, in hot ethanol, and in hot methanol.

Identification—

A: Dissolve about 10 mg. of Diethylstilbestrol Dipropionate in 2 ml. of sulfuric acid: an orange color is produced which disappears on dilution with water.

B: Add 1 ml. of a solution of antimony pentachloride in dry, alcohol-free chloroform (1 in 2) to 5 ml. of a dilute solution of Diethylstilbestrol Dipropionate in the same solvent: a red-colored solution is produced.

C: The diethylstilbestrol obtained in the *Assay* melts between 168° and 172°, page 814.

Melting range, page 814—Diethylstilbestrol Dipropionate melts between 105° and 107°.

Loss on drying, page 814—Dry Diethylstilbestrol Dipropionate to constant weight at 80° in vacuum: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Diethylstilbestrol Dipropionate yields not more than 0.05 percent of residue on ignition.

Assay—Dissolve about 300 mg. of Diethylstilbestrol Dipropionate, accurately weighed, in 10 ml. of a solution of potassium hydroxide in methanol (15 in 100), and reflux the solution for 30 minutes. Cool, dilute with 100 ml. of water, transfer the solution to a separator, and acidify it with diluted hydrochloric acid. Extract the mixture with three 20-ml. portions and two 10-ml. portions of ether, and wash the combined ether extracts with three 5-ml. portions of sodium bicarbonate solution (1 in 20) and one 5-ml. portion of water. Filter the washed ether extracts through an ether-washed pledget of cotton into a tared beaker, rinse the separator with two 5-ml. portions of ether, and pass the rinsings through the cotton, collecting the ether in the beaker. Evaporate the ether in a current of warm air, and dry the residue at 80° to constant weight. The weight of diethylstilbestrol so obtained, multiplied by 1.418, represents the weight of $C_{24}H_{28}O_4$ in the sample taken.

Packaging and storage—Preserve Diethylstilbestrol Dipropionate in tight containers.

CATEGORY—Estrogen.

USUAL DOSE RANGE—**100 mcg.** to **1 mg.** per day.

Diethylstilbestrol Dipropionate Tablets

Diethylstilbestrol Dipropionate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{24}H_{28}O_4$.

Identification—The solution prepared from Diethylstilbestrol Dipropionate Tablets for measurement of absorbance in the *Assay* exhibits a maximum at about 520 mμ.

Disintegration, page 878—The disintegration time limit for Diethylstilbestrol Dipropionate Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Diethylstilbestrol Dipropionate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Vanadyl sulfate solution—Dissolve about 100 mg. of vanadyl sulfate in 20 ml. of sulfuric acid in a 200-ml. volumetric flask, cautiously add glacial acetic acid to volume, and mix.

Standard preparation—Dissolve 80 mg. of USP Diethylstilbestrol Reference Standard, accurately weighed, in sufficient diluted alcohol to make 100.0 ml., and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with diluted alcohol, and mix.

Assay preparation—Weigh and finely powder not less than 50 Diethylstilbestrol Dipropionate Tablets. Transfer to a 50-ml. volumetric flask an accurately weighed portion of the powder, equivalent to about 14 mg. of diethylstilbestrol dipropionate, add 25 ml. of solvent hexane, and shake mechanically for 15 minutes. Dilute to volume with solvent hexane, mix, and centrifuge a portion of the mixture. Transfer to a 50-ml. conical flask 10.0 ml. of the clear, supernatant liquid, add 10 ml. of a solution of potassium hydroxide in alcohol (1 in 100), and evaporate the solvent hexane on a steam bath in a current of warm air. Reflux for 1 hour, cool, then transfer the solution to a 250-ml. separator, with the aid of 100 ml. of water. Acidify the solution to litmus with diluted hydrochloric acid, and extract with three 20-ml. portions and two 10-ml. portions of ether. Wash the combined ether extracts with three 5-ml. portions of sodium bicarbonate solution (1 in 20) and finally with 5 ml. of water. Filter the washed ether extracts through ether-washed cotton into a 250-ml. beaker, and evaporate the ether on a steam bath in a current of warm air. Dissolve the residue in diluted alcohol, transfer the solution to a 25-ml. volumetric flask, dilute to volume with diluted alcohol, and mix.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate test tubes fitted with glass stoppers and marked at the 5-ml. level. For a blank, place in a similar tube 2 ml. of diluted alcohol. Cautiously evaporate the liquids to dryness on a steam bath. Add to each test tube 5.0 ml. of the *Vanadyl sulfate solution*, stopper loosely, and heat on a steam bath for 1 hour. Cool, shake well, allow to stand for 5 minutes, add water, if necessary, to the 5-ml. level, and mix. Concomitantly determine the absorbance of each solution in 1-cm. cells, at 520 mμ, with a suitable spectrophotometer, setting the instrument at zero absorbance with the blank. Record the absorbance from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{24}H_{28}O_4$ in the portion of the Tablets taken by the formula $0.125C \times 1.418 \times (A_U/A_S)$, in which C is the exact quantity, in mcg., of USP Diethylstilbestrol Reference Standard per ml. of the *Standard preparation*, and 1.418 is the factor converting diethylstilbestrol to diethylstilbestrol dipropionate.

Packaging and storage—Preserve Diethylstilbestrol Dipropionate Tablets in tight containers.

Tablets available—Diethylstilbestrol Dipropionate Tablets usually available contain the following amounts of diethylstilbestrol dipropionate: 500 mcg., 1 mg., and 5 mg.

CATEGORY and DOSE—See Diethylstilbestrol Dipropionate.

Digitalis Capsules

Digitalis Capsules contain an amount of powdered digitalis equivalent to not less than 85.0 percent and not more than 120.0 percent of the labeled potency.

Weight variation, page 901—Digitalis Capsules meet the requirements of the weight variation test for capsules.

Salmonella, page 862—The test for *Salmonella* in Digitalis Capsules is negative.

Assay—

Standard preparation—Weigh the contents of one container of USP Digitalis Reference Standard to the nearest mg., either in the original container or in a weighing bottle, and transfer to a dry, hard-glass, glass-stoppered container of at least 50-ml. capacity. Complete the weighing within 5 minutes after opening the ampul. Add sufficient menstruum consisting of 4 parts of alcohol, by volume, and 1 part of water, by volume, so that the total volume of menstruum added corresponds to 10 ml. for each g. of powder. Insert the stopper, the upper third of which is greased lightly with petrolatum. Shake the mixture for 24 hours ± 2 hours at 25° ± 5° by mechanical means which continuously brings the solid material into fresh contact with the liquid phase. Immediately thereafter, centrifuge the mixture, decant into a dry, hard-glass bottle having a tight closure, and preserve under refrigeration until used. Use within 30 days.

Assay preparation—

CAPSULES OF DRY POWDERED DIGITALIS—Empty the contents of not less than 20 Digitalis Capsules into a hard-glass, glass-stoppered container of at least 50-ml. capacity. Add a menstruum consisting of 4 parts of alcohol, by volume, and 1 part of water, by volume, so that the total volume of menstruum corresponds to 1 ml. for each expected USP Digitalis Unit. Insert the stopper, the upper third of which is greased lightly with petrolatum. Shake the mixture for 24 hours ± 2 hours at 25° ± 5° by mechanical means which continuously brings the solid material into fresh contact with the liquid phase. Immediately thereafter transfer to a centrifuge tube, centrifuge, and decant into a dry, hard-glass bottle having a tight closure. Preserve under refrigeration until used. Use within 30 days.

CAPSULES OF DIGITALIS SUSPENDED IN WATER-IMMISCIBLE MEDIA (OIL, FAT, WAX, ETC.)—Cut not less than 20 Digitalis Capsules into halves in a dry, shallow glass container. Transfer the contents, together with the capsules, quantitatively, with the aid of a sufficient amount of solvent hexane to a dry, hard-glass, glass-stoppered container of suitable capacity. Add solvent hexane to make a volume approximately 3 times the volume occupied by the capsule fragments and the contents of the capsules. Shake vigorously and centrifuge. Decant and discard the solvent hexane extract. Repeat the solvent hexane extraction twice. Place the extraction container with its contents, with the stopper removed, in an oven at 60° for 8 hours. Remove it from the oven, allow it to cool, and add menstruum consisting of 4 parts of alcohol, by volume, and 1 part of water, by volume, so that the total volume of menstruum corresponds to 1 ml. for each expected USP Digitalis Unit. Insert the stopper, the upper third of which is greased lightly with petrolatum. Shake the mixture for 24 hours ± 2 hours at 25° ± 5° by mechanical means which continuously brings the solid material into fresh contact with the liquid phase. Immediately thereafter transfer to a centrifuge tube, centrifuge the mixture, and decant into a dry, hard-glass bottle having a tight closure. Preserve under refrigeration until used. Use within 30 days.

The pigeons—Employ adult pigeons free from gross evidence of disease or emaciation, and of such weight that the heaviest weighs less than twice the weight of the lightest. Divide the pigeons into groups as nearly alike as practicable with respect to breed and weight so that the average weight of the group assigned by random choice to the *Standard preparation* shall not differ by more than 30% from the average weight of the group assigned to the preparation to be assayed. Withhold food but not water during the period 16 to 28 hours prior to use. Preparatory to injection, lightly anesthetize the pigeon with ether and immobilize it; expose an alar vein and cannulate with a suitable metal or glass cannula. Maintain the anesthesia during cannulation and throughout the subsequent injection period at such a level that pain is absent, the pupillary and corneal reflexes are present, and the voluntary musculature is not relaxed beyond permitting the pigeon to make some voluntary movement occasionally.

Preparation of the test dilutions—Dilute the *Standard preparation* and the preparation to be assayed (*Assay preparation*) with isotonic sodium chloride solution in such a way that the estimated fatal dose of each preparation will be 15 ml. per kg. of pigeon. Make test dilutions the day they are to be used.

Injection of the test dilutions—Arrange to inject the appropriate test dilution by suitable means such as a small-bore buret calibrated to 0.05 ml. Start the injection after insuring the absence of air bubbles from the injection apparatus, by infusing, within a few seconds, a volume of the test dilution equivalent to 1 ml. per kg. of body weight of the pigeon. Repeat this dose at 5-minute intervals thereafter until the pigeon dies of cardiac arrest.

Use a total of not less than 6 pigeons for the *Standard preparation* and not less than 6 pigeons for the preparation to be assayed. If the average number of doses for any given dilution required to produce death is less than 13 or greater than 19, or if the larger exceeds the smaller in the same assay by more than 4 doses, regard these data as preliminary. Use them as a guide, and repeat with a fresh, higher, or lower dilution. Complete the assay within a period of 30 days.

Calculation of the potency—For the group of pigeons injected with the *Standard preparation* find the average of the number of doses of test dilution which were injected and designate it $\bar{y}_S$; similarly find the average of the number of doses of the preparation to be assayed and designate it $\bar{y}_U$. The value of the ratio,

$$\frac{\bar{y}_S \times \text{No. of ml. of } \textit{Standard preparation} \text{ in 100 ml. of test dilution}}{\bar{y}_U \times \text{No. of ml. of preparation to be assayed in 100 ml. of test dilution}}$$

is the potency in USP Digitalis Units per ml.

For the group of pigeons injected with the *Standard preparation* find the range of the number of doses of the test dilution which were injected by subtracting the smallest from the largest number and designate it R_S; similarly find the range for the preparation to be assayed and designate it R_U. Determine the value of g corresponding to the number of pigeons used respectively on the *Standard preparation* (g_S) and the preparation to be assayed (g_U) from the following table:

Number of pigeons:	6	7	8	9	10
Value of *g*:	.026	.019	.015	.013	.011

Number of pigeons:	11	12	13	14
Value of *g*:	.0090	.0078	.0069	.0062

Using these values and those obtained in the calculation of the potency, calculate the standard error of the assay in terms of USP Digitalis Units per ml. by the following formula:

$$\text{standard error of the assay} = \text{Potency}\sqrt{g_S\left(\frac{R_S}{\bar{y}_S}\right)^2 + g_U\left(\frac{R_U}{\bar{y}_U}\right)^2}$$

If the standard error exceeds 0.08 USP Digitalis Unit per ml., repeat the assay or use more pigeons on either the *Standard preparation* or the preparation to be assayed or both until the standard error falls within the limit of 0.08 USP Digitalis Unit per ml.

Packaging and storage—Preserve Digitalis Capsules in well-closed containers.

Capsules available—Digitalis Capsules usually available contain the following amounts of digitalis: 60 and 100 mg.

Category—Cardiotonic.

Usual dose of powdered digitalis—Initial, **1.5 g.** divided over 24 to 48 hours. Maintenance, **100 mg.** daily.

Digitoxin Injection

Digitoxin Injection is a sterile solution of digitoxin in 5 to 50 percent (v/v) of alcohol, and may contain glycerin or other suitable solubilizing agents. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{41}H_{64}O_{13}$.

Identification—

A: Evaporate 100 ml. of the chromatographic eluate obtained in the *Assay* on a steam bath, with the aid of a current of air, to dryness. Dissolve the residue in 2 ml. of a solution prepared by mixing 0.3 ml. of ferric chloride T.S. and 50 ml. of glacial acetic acid, and underlay with 2 ml. of sulfuric acid: at the zone of contact of the two liquids a brown color, which gradually changes to light green, then to blue, is produced, and finally the entire acetic acid layer acquires a blue color.

B: Transfer 20 ml. of the chromatographic eluate obtained in the *Assay* to a small flask, and evaporate on a steam bath, with the aid of a current of air, to dryness. Add 2 ml. of a freshly prepared 1 in 100 solution of *m*-dinitrobenzene in alcohol, and allow to stand for 10 minutes with frequent shaking. Add 2 ml. of a 1 in 200 solution of tetramethylammonium hydroxide in alcohol, and mix: a red-violet color develops slowly and then fades.

Other requirements—Digitoxin Injection meets the requirements under *Injections*, page 810.

Assay—

Adsorbent—Boil a mixture of 150 g. of chromatographic siliceous earth and 1000 ml. of diluted hydrochloric acid for 10 minutes. Cool, filter by suction, wash thoroughly with water until the last washing is neutral to methyl orange T.S., dry at 105° overnight, and ignite at 500° for 2 hours.

Benzene-chloroform mixture (mobile solvent)—Mix 300 ml. of benzene and 100 ml. of chloroform.

Chromatographic tube—Insert a small pledget of glass wool at the juncture of the tube and the stem of a chromatographic tube which is about 200 mm. long and about 25 mm. in internal diameter, and place a plug of purified cotton above the juncture. Arrange a long-stemmed, glass-stoppered, 500-ml. separator to serve as a reservoir for maintaining a constant level of liquid in the tube.

Chromatographic column—Mix about 2 g. of the *Adsorbent* with 1 ml. of water in a 100-ml. beaker until the mixture appears fluffy and uniformly moistened, and transfer to the chromatographic tube, pressing down lightly with a packing rod to a thickness of 15 to 20 mm. Mix uniformly about 3 g. of *Adsorbent* with a mixture of 2 ml. of formamide and 1 ml. of water, and transfer to the chromatographic tube. Introduce a pledget of purified cotton, and press it down lightly and evenly, sweeping the wall of the tube with it.

Standard preparation—Dissolve in alcohol 20.0 mg. of USP Digitoxin Reference Standard, previously dried in vacuum at 100° for 2 hours, dilute with alcohol to 50.0 ml., and mix. Pipet 5.0 ml. of the solution into a 50-ml. volumetric flask, dilute to volume with alcohol, and mix.

Assay preparation—Transfer an accurately measured volume of Digitoxin Injection, equivalent to about 2 mg. of digitoxin, to a separator containing 40 ml. of water and 1 ml. of diluted sulfuric acid. Extract with four 25-ml. portions of chloroform, washing the chloroform extracts in succession in a second separator containing 10 ml. of water. Filter the washed chloroform extract through chloroform-washed cotton, into a 250-ml. beaker, and evaporate on a steam bath, with the aid of a current of air, to dryness. Add 4 ml. of formamide, and warm on the steam bath for 20 minutes, stirring frequently. Cool, add 4 ml. of water and about 8 g. of *Adsorbent*, and mix until the mass appears uniform and does not adhere to the beaker.

Procedure—Transfer the *Assay preparation* in portions through a powder funnel to a prepared *Chromatographic column*, sweeping particles adhering to the beaker or funnel into the tube with a rubber-tipped rod. Scrub the beaker and stirring rod with about 500 mg. of *Adsorbent*, and add it to the tube through the funnel. Repeat the scrubbing with two additional 500-mg. portions of *Adsorbent*. Place a pledget of purified cotton in the tube, and press it down on the column with a packing rod, sweeping the wall of the tube with it so that the over-all height of the column is between 120 and 150 mm. Elute the digitoxin with the *Benzene-chloroform mixture*. Collect nearly 250 ml. of eluate, at a rate not exceeding 4 ml. per minute. Wash the stem of the tube with a stream of chloroform, dilute to 250.0 ml. with chloroform, and mix.

Pipet 25.0 ml. of the eluate mixture and 5.0 ml. of the *Standard preparation* into separate 50-ml. conical flasks, and evaporate on a steam bath, with the aid of a current of air, to dryness. Moisten each residue with about 0.5 ml. of alcohol, and again evaporate to dryness. Cool, pipet 5.0 ml. of alcohol into each flask, stopper, and allow to stand for 15 minutes at 25 ± 3°, with occasional shaking to effect solution. Pipet 5.0 ml. of alcohol into a similar flask, to serve as a blank, and treat all three flasks as follows:

Add 3.0 ml. of alkaline picrate T.S., and mix by swirling, maintaining the temperature at 25 ± 3°. Protect the mixture from intense light. After 16 minutes determine the absorbances of the solutions, in 1-cm. cells, at 495 mμ, with a suitable spectrophotometer, using the blank to set the instrument.

Calculate the quantity, in mg., of $C_{41}H_{64}O_{13}$ in each ml. of the Injection taken by the formula $(2/V) \times (A_U/A_S)$, in which V is the volume, in ml., of the Injection taken, A_U is the absorbance of the solution from the *Assay preparation*, and A_S is that from the *Standard preparation*.

Alcohol content, page 772—Digitoxin Injection contains not less than 90 percent and not more than 110 percent (v/v) of the labeled percent of C_2H_5OH.

Packaging and storage—Preserve Digitoxin Injection in single-dose or multiple-dose containers, preferably in Type I glass, protected from light.

Injections available—Digitoxin Injection usually available contains the following amounts of digitoxin: 100 and 200 mcg. in 1 ml.

CATEGORY—Cardiotonic.

USUAL DOSE RANGE OF DIGITOXIN—Intravenous—Initial, **500 mcg.** to **1.2 mg.**; maintenance, **100** to **200 mcg.**

Dihydroxyaluminum Aminoacetate

$NH_2CH_2COOAl(OH)_2 . xH_2O$

(Glycinato)dihydroxyaluminum

$C_2H_6AlNO_4 . xH_2O$ Mol. wt. (anhydrous) 135.05

Dihydroxyaluminum Aminoacetate yields not less than 35.5 percent and not more than 38.5 percent of Al_2O_3 (aluminum oxide), calculated on the dried basis. Dihydroxyaluminum Aminoacetate may contain small amounts of aluminum oxide and of aminoacetic acid.

Description—Dihydroxyaluminum Aminoacetate occurs as a white, odorless powder. It has a faintly sweet taste.

Solubility—Dihydroxyaluminum Aminoacetate is insoluble in water and in organic solvents. It dissolves in dilute mineral acids and in solutions of fixed alkalies.

Identification—Suspend 1 g. of Dihydroxyaluminum Aminoacetate in 25 ml. of water, add hydrochloric acid, dropwise, until a clear solution is formed, and divide it into two equal parts for the following tests.

A: One portion of the solution responds to the tests for *Aluminum*, page 807.

B: To the other portion of the solution, add 1 drop of liquefied phenol and 5 ml. of sodium hypochlorite T.S.: a blue color is produced.

pH, page 824—The pH of a suspension of 1 g. of finely powdered Dihydroxyaluminum Aminoacetate in 25 ml. of water is between 6.5 and 7.5.

Loss on drying, page 814—Dry Dihydroxyaluminum Aminoacetate to constant weight at 130°: it loses not more than 14.5 percent of its weight.

Acid-consuming capacity—Transfer 250.0 mg. of finely powdered Dihydroxyaluminum Aminoacetate to a flask containing 50.0 ml. of 0.1 *N* hydrochloric acid, and allow the mixture to stand for 10 minutes with occasional agitation. Titrate the excess hydrochloric acid with 0.1 *N* sodium hydroxide, using bromophenol blue T.S. as the indicator: 1 g. of Dihydroxyaluminum Aminoacetate consumes not less than 140 ml. of 0.1 *N* hydrochloric acid.

Acid-neutralizing capacity—Transfer 200.0 mg. of finely powdered Dihydroxyaluminum Aminoacetate to a flask containing 25 ml. of 0.1 *N* hydrochloric acid and shake the mixture vigorously for 5 minutes. At the end of 10 minutes the pH of the mixture is above 3.0.

Mercury—Dissolve completely 1 g. of Dihydroxyaluminum Aminoacetate in 10 ml. of diluted hydrochloric acid, and shake the solution formed with 10 ml. of a solution of dithizone in carbon tetrachloride (1 in 500): no orange color develops in the carbon tetrachloride layer.

Isopropyl alcohol—Transfer about 5 g. of Dihydroxyaluminum Aminoacetate to a flask provided with a reflux condenser, add 100 ml. of approximately 0.1 *N* potassium permanganate and 10 ml. of sulfuric acid. Reflux the mixture for 30 minutes, distil, and collect 10 ml. of the distillate. To 1 ml. of the distillate add 5 drops of sodium nitroferricyanide T.S. and 2 ml. of sodium hydroxide T.S., and then add a slight excess of acetic acid: no red color is produced.

Nitrogen—Determine the nitrogen content of Dihydroxyaluminum Aminoacetate, as directed under *Nitrogen Determination, Method II*, page 821, using about 100 mg., previously dried at 130° to constant weight and accurately weighed. Each ml. of 0.1 *N* sulfuric acid is equivalent to 1.401 mg. of nitrogen. The amount of nitrogen found is not less than 9.9 percent and not more than 10.6 percent.

Assay—Transfer about 2.5 g. of Dihydroxyaluminum Aminoacetate, accurately weighed, to a 150-ml. beaker, add 15 ml. of hydrochloric acid, and warm if necessary to completely dissolve the sample. Transfer the solution quantitatively, with the aid of water, to a 500-ml. volumetric flask, dilute to volume with water, and mix. Pipet 20.0 ml. of this solution into a 250-ml. beaker, and add, in the order named and with continuous stirring, 25.0 ml. of 0.05 *M* disodium ethylenediaminetetraacetate and 20 ml. of acetic acid-ammonium acetate buffer T.S., then heat the solution near the boiling point for 5 minutes. Cool, and add 50 ml. of alcohol, and 2 ml. of dithizone T.S. Titrate with 0.05 *M* zinc sulfate until the color changes from green-violet to rose-pink. Perform a blank determination, substituting 20 ml. of water for the sample solution, and make any necessary correction. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 2.549 mg. of Al_2O_3.

Packaging and storage—Preserve Dihydroxyaluminum Aminoacetate in well-closed containers.

CATEGORY—Antacid.

USUAL DOSE—**500 mg.** to **1 g.** four times a day.

USUAL DOSE RANGE—**500 mg.** to **2 g.**

Dihydroxyaluminum Aminoacetate Magma

Dihydroxyaluminum Aminoacetate Magma is a suspension which yields an amount of Al_2O_3 (aluminum oxide) equivalent to not less than 28.5 percent and not more than 35.0 percent of the labeled amount of $C_2H_6AlNO_4$.

Description—Dihydroxyaluminum Aminoacetate Magma is a white, viscous suspension, from which small amounts of water may separate on standing.

Identification—Dilute a volume of Dihydroxyaluminum Aminoacetate Magma, equivalent to 1 g. of dihydroxyaluminum aminoacetate, to 25 ml. with water, add hydrochloric acid, dropwise, until a solution results, and then filter: the filtered solution responds to the *Identification tests* under *Dihydroxyaluminum Aminoacetate,* page 236.

pH, page 824—The pH of a dilution of Dihydroxyaluminum Aminoacetate Magma in water, equivalent to 1 g. of dihydroxyaluminum aminoacetate in 25 ml., is between 6.5 and 7.5.

Acid-consuming capacity—Transfer a volume of Dihydroxyaluminum Aminoacetate Magma, equivalent to about 250 mg. of dihydroxyaluminum aminoacetate, to a 125-ml. glass-stoppered conical flask containing 50.0 ml. of 0.1 *N* hydrochloric acid, and proceed as directed in the test for *Acid-consuming capacity* under *Dihydroxyaluminum Aminoacetate,* page 236, beginning with "... allow the mixture to stand for 10 minutes ...." The amount of 0.1 *N* hydrochloric acid consumed is not less than 125 ml. and not more than 175 ml. for each g. of dihydroxyaluminum aminoacetate present in the sample used for the test.

Acid-neutralizing capacity—Transfer an amount of Dihydroxyaluminum Aminoacetate Magma, equivalent to 200 mg. of dihydroxyaluminum aminoacetate, to a 125-ml. glass-stoppered conical flask containing 25 ml. of 0.1 *N* hydrochloric acid, stopper the flask, shake vigorously during 5 minutes, and allow the mixture to stand for 10 minutes: the pH of the mixture is above 3.0.

Assay—(Shake the container mechanically for 1 hour before removing the sample.) Weigh accurately in a tared beaker a quantity of Dihydroxyaluminum Aminoacetate Magma, equivalent to about 2.5 g. of dihydroxyaluminum aminoacetate, add 15 ml. of hydrochloric acid, and boil gently for about 5 minutes. Cool and transfer the solution quantitatively, with the aid of water, to a 500-ml. volumetric flask, dilute to volume with water, mix, and filter, if necessary, to obtain a clear solution. Proceed as directed in the *Assay* under *Dihydroxyaluminum Aminoacetate,* page 236, beginning with "Pipet 20.0 ml. of this solution ...."

Packaging and storage—Preserve Dihydroxyaluminum Aminoacetate Magma in tight containers and protect it from freezing.

CATEGORY and DOSE—See Dihydroxyaluminum Aminoacetate.

Dihydroxyaluminum Aminoacetate Tablets

Dihydroxyaluminum Aminoacetate Tablets yield an amount of Al_2O_3 (aluminum oxide) equivalent to not less than 28.5 percent and not more than 35.0 percent of the labeled amount of $C_2H_6AlNO_4$.

Identification—Weigh and finely powder not less than 20 Dihydroxyaluminum Aminoacetate Tablets. Suspend a portion of the powder, equivalent to about 1 g. of dihydroxyaluminum aminoacetate, in 25 ml. of water, add hydrochloric acid, dropwise, until all the dihydroxyaluminum aminoacetate is dissolved, and filter. The solution responds to the *Identification tests* under *Dihydroxyaluminum Aminoacetate,* page 236. Retain the remaining portion of the powder for the following tests as indicated.

pH, page 824—The pH of a suspension of an accurately weighed quantity of the powder, retained in the *Identification test,* equivalent to 1 g. of dihydroxyaluminum aminoacetate in 25 ml. of water is between 6.5 and 7.5.

Acid-consuming capacity—Proceed with Dihydroxyaluminum Aminoacetate Tablets as directed in the test for *Acid-consuming capacity* under *Dihydroxyaluminum Aminoacetate,* page 236, using an amount of the powder, retained in the *Identification test,* equivalent to 250 mg. of dihydroxyaluminum aminoacetate.

Acid-neutralizing capacity—Dihydroxyaluminum Aminoacetate Tablets meet the requirements of the test for *Acid-neutralizing capacity* under *Dihydroxyaluminum Aminoacetate,* page 236, using an amount of the powder, retained in the *Identification test,* equivalent to 200 mg. of dihydroxyaluminum aminoacetate.

Disintegration, page 878—The disintegration time limit for Dihydroxyaluminum Aminoacetate Tablets is 30 minutes.

Weight variation, page 901—Dihydroxyaluminum Aminoacetate Tablets meet the requirements of the weight variation test for tablets.

Assay—Transfer to a flask an accurately weighed portion of the powder, retained in the *Identification test,* equivalent to about 2.5 g. of dihydroxyaluminum aminoacetate, add 15 ml. of hydrochloric acid and 10 ml. of water, and boil gently for about 5 minutes. Cool and transfer the solution quantitatively, with the aid of water, to a 500-ml. volumetric flask, dilute to volume with water, mix, and filter to obtain a clear solution. Proceed as directed in the *Assay* under *Dihydroxyaluminum Aminoacetate,* page 236, beginning with "Pipet 20.0 ml. of this solution. . . ."

Packaging and storage—Preserve Dihydroxyaluminum Aminoacetate Tablets in well-closed containers.

Tablets available—Dihydroxyaluminum Aminoacetate Tablets usually available contain the following amount of dihydroxyaluminum aminoacetate: 500 mg.

CATEGORY and DOSE—See Dihydroxyaluminum Aminoacetate.

Dihydroxyaluminum Sodium Carbonate*

$(HO)_2AlOCO_2Na . xH_2O$

Aluminum Sodium Carbonate Hydroxide

$CH_2AlNaO_5 . xH_2O$ Mol. wt. (anhyd.) 144.00

Dihydroxyaluminum Sodium Carbonate, dried to constant weight at 130°, contains the equivalent of not less than 34.8 percent and not more than 38.2 percent of Al_2O_3 (aluminum oxide), and the equivalent of not less than 28.5 percent and not more than 31.5 percent of CO_2 (carbon dioxide).

Description—Dihydroxyaluminum Sodium Carbonate occurs as a fine, white, odorless powder.

Solubility—Dihydroxyaluminum Sodium Carbonate is practically insoluble in water and in organic solvents. It dissolves in dilute mineral acids with the evolution of carbon dioxide.

Identification—A 1 in 20 suspension of Dihydroxyaluminum Sodium Carbonate in diluted hydrochloric acid responds to the tests for *Aluminum*, page 807, and for *Sodium*, page 810.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dihydroxyaluminum Sodium Carbonate, previously dried to constant weight at 130°, exhibits maxima only at the same wavelengths as that of NF Dihydroxyaluminum Sodium Carbonate Reference Standard, similarly measured.

pH, page 824—The pH of a 1 in 25 suspension of Dihydroxyaluminum Sodium Carbonate in water is between 9.9 and 10.2.

Acid-consuming capacity—Mix about 250 mg. of Dihydroxyaluminum Sodium Carbonate, accurately weighed, with 100.0 ml. of 0.1 *N* hydrochloric acid, and stir with a magnetic stirrer until the sample is completely dissolved. Using a suitable electrode system, titrate the excess acid with 0.1 *N* sodium hydroxide to a pH of 3.8: the volume of 0.1 *N* acid consumed is not less than 230 ml. for each g. of Dihydroxyaluminum Sodium Carbonate.

Acid-neutralizing capacity—Mix 200.0 mg. of Dihydroxyaluminum Sodium Carbonate with 25.0 ml. of 0.1 *N* hydrochloric acid, and allow to stand for exactly 10 minutes: the pH is not less than 3.0.

Prolonged neutralization—Mix 1.000 g. of Dihydroxyaluminum Sodium Carbonate with 25.0 ml. of 0.1 *N* hydrochloric acid, stir with a magnetic stirrer for 1 minute, and then record the pH. Continue adding 0.1 *N* hydrochloric acid at the rate of 1 ml. per minute, preferably with an automatic buret, for a period of 2 hours: the final pH is not less than 3.0.

Loss on drying, page 814—Dry Dihydroxyaluminum Sodium Carbonate to constant weight at 130°: it loses not more than 14 percent of its weight.

Isopropyl alcohol—

Standard isopropyl alcohol solution and *Factor determination*—Dilute about 500 mg. of isopropyl alcohol, accurately weighed, to 500.0 ml. with water, calculate the weight, in mg., of isopropyl alcohol per ml. of the solution, and record this value as W. Transfer 5.0 ml. of this solution to a 500-ml. iodine flask, add 50 ml. of dilute sulfuric acid (1 in 2) and 5.0 ml. of 0.07 *N* potassium dichromate, and heat in a boiling water bath for 15 minutes with the flask loosely stoppered. Remove the flask from the water bath, cool slightly, add 225 ml. of water, 5 ml. of phosphoric acid, 10.0 ml. of 0.05 *N* ferrous ammonium sulfate, and 10 drops of diphenylamine T.S., and titrate with 0.07 *N* potassium dichromate to a permanent purple color. Calculate the factor, F, by the formula $W/[(V_1 \times N_1) - (10 \times N_2)]$, in which V_1 is the total volume, in ml., and N_1 is the exact normality, respectively, of the potassium dichromate solution, and N_2 is the exact normality of the ferrous ammonium sulfate solution.

Procedure—Transfer about 500 mg. of Dihydroxyaluminum Sodium Carbonate, accurately weighed, to a 500-ml. iodine flask, slowly add 10 ml. of dilute sulfuric acid (1 in 2), swirl to dissolve, and then add 5.0 ml. of 0.07 *N* potassium dichromate. Heat in a boiling water bath for 15 minutes with the flask loosely stoppered, remove the flask from the water bath, and cool slightly. Add 225 ml. of water, 5 ml.

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* Patented. See notice, page ii.

of phosphoric acid, 10.0 ml. of 0.05 *N* ferrous ammonium sulfate, and 10 drops of diphenylamine T.S., and titrate with 0.07 *N* potassium dichromate to a permanent purple color. Calculate the percent of isopropyl alcohol in the sample taken by the formula $F \times [(V_1 \times N_1) - (10 \times N_2)]$: not more than 1 percent is found.

Mercury—Dissolve 1 g. of Dihydroxyaluminum Sodium Carbonate, accurately weighed, in 10 ml. of 3 *N* sulfuric acid contained in a glass-stoppered flask, add 5 ml. of a 1 in 100,000 solution of dithizone in carbon tetrachloride, and shake vigorously for 1 minute: no orange or yellow color develops within 2 minutes.

Assay for aluminum oxide—Transfer about 200 mg. of Dihydroxyaluminum Sodium Carbonate, previously dried at 130° to constant weight and accurately weighed, to a 250-ml. beaker, add 10 ml. of diluted nitric acid, cover the beaker, and boil for 1 minute. Add 25.0 ml. of 0.1 *M* disodium ethylenediaminetetraacetate, again boil for 1 minute and cool, then add 10 ml. of acetic acid–ammonium acetate buffer T.S., 50 ml. of acetone, and 2 ml. of dithizone T.S. Using a pH meter, adjust the pH to 4.5 by the addition of stronger ammonia T.S., and titrate with 0.05 *M* zinc nitrate, maintaining the pH at 4.5 by the addition of stronger ammonia T.S. as necessary, to an orange-pink color. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* disodium ethylenediaminetetraacetate is equivalent to 5.098 mg. of Al_2O_3.

Assay for carbon dioxide—

Apparatus—Assemble an apparatus consisting of a 250-ml. conical flask to which is attached, by way of a connecting tube, a separator. Attach a condenser to the flask, then to the condenser attach, by way of connecting tubes, a train of 3 absorption bulbs. Partly fill the first bulb with sulfuric acid; fill the second bulb with porous, granular anhydrous calcium sulfate; fill the third bulb three-fourths full with 20-mesh indicating carbon dioxide absorbent and the remaining one-fourth with the porous, granular anhydrous calcium sulfate. Connect the end of this train to a vacuum line.

Procedure—Transfer about 800 mg. of Dihydroxyaluminum Sodium Carbonate, previously dried at 130° to constant weight, accurately weighed, to the 250-ml. conical flask, add 50 ml. of water and 1 boiling chip, and assemble the apparatus. Position the separator so that its stem extends below the level of water in the flask. Close the stopcock of the separator, to it add 25 ml. of dilute hydrochloric acid (1 in 4), and then stopper the funnel with a small tube filled with 20-mesh indicating carbon dioxide absorbent. Weigh accurately the second bulb in the absorption train, and then connect the bulb back into the system. Open the stopcock of the separator (Caution: Do not close the stopcock during the remainder of the procedure), and apply and maintain a gentle vacuum. When the initial evolution of carbon dioxide gas has ceased, heat the contents of the flask to boiling to expel the dissolved carbon dioxide, and boil gently for 5 minutes. Remove the heat, and allow air to be drawn slowly through the system for 30 minutes. Remove the second absorption bulb, weigh accurately: the difference between the initial and final weighings of the bulb represents the weight of CO_2 in the sample taken.

Packaging and storage—Preserve Dihydroxyaluminum Sodium Carbonate in tight containers.

CATEGORY—Antacid.

USUAL DOSE RANGE—**300** to **600 mg.** as required.

Dihydroxyaluminum Sodium Carbonate Tablets

Dihydroxyaluminum Sodium Carbonate Tablets contain an amount of Al_2O_3 (aluminum oxide) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of CH_2AlNaO_5.

Identification—A 1 in 10 suspension of powdered Dihydroxyaluminum Sodium Carbonate Tablets in diluted hydrochloric acid responds to the tests for *Aluminum*, page 807, and for *Sodium*, page 810.

Weight variation, page 901—Dihydroxyaluminum Sodium Carbonate Tablets meet the requirements of the weight variation test for tablets.

Acid-consuming capacity—Dissolve 1 Dihydroxyaluminum Sodium Carbonate Tablet in 100.0 ml. of 0.1 *N* hydrochloric acid, stirring vigorously for 15 to 20 minutes. Titrate the excess acid with 0.1 *N* sodium hydroxide to a pH of 3.8: the volume of 0.1 *N* acid consumed is not less than 75 ml.

Assay for aluminum oxide—Weigh and finely powder not less than 20 Dihydroxyaluminum Sodium Carbonate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg. of dihydroxyaluminum sodium carbonate, to a 250-ml. beaker and continue as directed in the *Assay for aluminum oxide* under *Dihydroxyaluminum Sodium Carbonate*, page 239, beginning with "... add 10 ml. of diluted nitric acid ..." Each ml. of 0.1 *M* disodium ethylenediaminetetraacetate is equivalent to 5.098 mg. of Al_2O_3, corresponding to 14.40 mg. of CH_2AlNaO_5.

Packaging and storage—Preserve Dihydroxyaluminum Sodium Carbonate Tablets in well-closed containers.

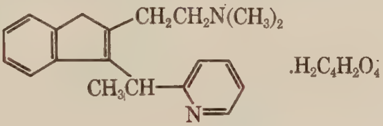
Tablets available—Dihydroxyaluminum Sodium Carbonate Tablets usually available are chewable tablets and contain the following amount of dihydroxyaluminum sodium carbonate (anhydrous): 300 mg.

Labeling—Label Dihydroxyaluminum Sodium Carbonate Tablets to indicate that they are to be chewed before swallowing.

CATEGORY and DOSE—See Dihydroxyaluminum Sodium Carbonate.

Diluted Acetic Acid, page 19
Diluted Erythrityl Tetranitrate, page 273
Diluted Hydrochloric Acid, page 350
Diluted Pentaerythritol Tetranitrate, page 526
Diluted Phosphoric Acid, page 552
Diluted Sodium Hypochlorite Solution, page 648

Dimethindene Maleate*



2-[1-[2-[2-(Dimethylamino)ethyl]inden-3-yl]ethyl]pyridine Maleate (1:1)

$C_{20}H_{24}N_2 . C_4H_4O_4$ Mol. wt. 408.50

Dimethindene Maleate contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{24}N_2 . C_4H_4O_4$, calculated on the dried basis.

Description—Dimethindene Maleate occurs as a white, crystalline powder having a characteristic odor. It melts with decomposition at about 161°.

Solubility—Dimethindene Maleate is sparingly soluble in water. It is soluble in chloroform, freely soluble in methanol, and insoluble in ether.

Identification—Dissolve about 5 mg. of Dimethindene Maleate in 10 ml. of alcohol in a glass-stoppered test tube, add 1 ml. of benzaldehyde and 1 ml. of tetramethylammonium hydroxide T.S., and heat on a steam bath about 30 minutes: a yellow color develops.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dimethindene Maleate, previously dried in vacuum at 60° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Dimethindene Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Dimethindene Maleate in 0.1 *N* sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Dimethindene Maleate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 258 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Dimethindene Maleate in vacuum at 60° for 4 hours: it loses not more than 0.1 percent of its weight.

Residue on ignition, page 858—Dimethindene Maleate yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 400 mg. of Dimethindene Maleate, accurately weighed, in 100 ml. of glacial acetic acid, add 3 drops of a 1 in 1000 solution of *p*-naphtholbenzein in glacial acetic acid, and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 20.42 mg. of $C_{20}H_{24}N_2 . C_4H_4O_4$.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Dimethindene Maleate in tight, light-resistant containers.

Category—Antihistaminic.

Usual dose range—**1** to **2 mg.** one to three times a day.

Dimethindene Maleate Syrup

Dimethindene Maleate Syrup contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{20}H_{24}N_2 . C_4H_4O_4$.

Identification—

A: The ultraviolet absorption spectrum of the *Assay preparation*, prepared as directed in the *Assay*, exhibits maxima and minima at the same wavelengths as that of the *Standard preparation*, prepared as directed in the *Assay*.

B: Transfer to a centrifuge tube a volume of Dimethindene Maleate Syrup, equivalent to about 2 mg. of dimethindene maleate, add an equal volume of sodium hydroxide T.S., and extract with two 10-ml. portions of chloroform. Filter the chloroform extracts through a pledget of glass wool, previously rinsed with chloroform, into a beaker, and evaporate the chloroform to dryness on a steam bath. Dissolve the residue in 10 ml. of alcohol, add 1 ml. of tetramethylammonium hydroxide T.S. and 0.5 ml. of benzaldehyde, and heat on a steam bath in a stoppered test tube for about 30 minutes: a yellow color develops.

Assay—

Standard preparation—Weigh accurately 20 mg. of NF Dimethindene Maleate Reference Standard, dissolve in water to make 100.0 ml., and mix. Transfer 10.0 ml. of this solution to a separator, and continue as directed under *Assay preparation*, beginning with "Add about 5 ml. of sodium hydroxide T.S. . . ." Use the resulting solution as directed in *Procedure*.

Assay preparation—Transfer an accurately measured volume of Dimethindene Maleate Syrup, equivalent to about 2 mg. of dimethindene maleate, to a separator. Add about 5 ml. of sodium hydroxide T.S., mix, and extract with three 20-ml. portions of chloroform, shaking each portion for at least 2 minutes. Filter the chloroform extracts through a pledget of glass wool washed with chloroform into a 100-ml. volumetric flask, add chloroform to volume, and mix.

Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 263 mμ, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{20}H_{24}N_2 . C_4H_4O_4$ in the portion of Syrup taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Dimethindene Maleate Syrup in well-closed, light-resistant containers, preferably at a temperature not exceeding 30°.

Syrup available—Dimethindene Maleate Syrup usually available contains the following amount of dimethindene maleate: 1 mg. in 5 ml.

Category and Dose—See Dimethindene Maleate.

Dimethindene Maleate Tablets

Dimethindene Maleate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{20}H_{24}N_2 . C_4H_4O_4$.

Identification—

A: Transfer an amount of powdered Dimethindene Maleate Tablets, equivalent to about 1.5 mg. of dimethindene maleate, to a centrifuge tube, add about 10 ml. of sodium hydroxide T.S., and mix. Extract the mixture with 10 ml. of chloroform. Filter the extract through a pledget of glass wool previously washed with chloroform into a 100-ml. volumetric flask, add chloroform to volume, and mix. The ultraviolet absorption spectrum of this solution exhibits maxima and minima at the same wavelengths as that of NF Dimethindene Maleate Reference Standard treated in the same manner as the sample.

B: Transfer an amount of powdered Dimethindene Maleate Tablets, equivalent to about 2 mg. of dimethindene maleate, to a centrifuge tube, add 10 ml. of sodium hydroxide T.S., and mix. Extract the solution with two 10-ml. portions of chloroform, and continue as directed in *Identification test B* under *Dimethindene Maleate Syrup*, beginning with "Filter the chloroform extracts. . . ."

Disintegration, page 878—The disintegration time limit for Dimethindene Maleate Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Dimethindene Maleate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer one tablet to a 100-ml. volumetric flask, and add about 50 ml. of 0.1 *N* sulfuric acid. Shake mechanically for about 10 minutes, and dilute to volume with 0.1 *N* sulfuric acid. Mix well and filter, discarding the first 20 ml. of filtrate. Dilute an accurately measured volume of the subsequent filtrate quantitatively and stepwise, if necessary, with 0.1 *N* sulfuric acid to provide a solution containing approximately 10 mcg. of dimethindene maleate per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Dimethindene Maleate Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 258 mμ, with a suitable spectrophotometer, using 0.1 *N* sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{20}H_{24}N_2 . C_4H_4O_4$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of dimethindene maleate in the tablet; D is the exact concentration, in mcg. per ml., of dimethindene maleate in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

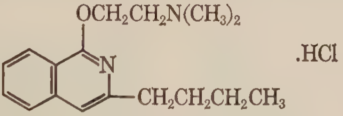
Assay—Weigh and finely powder not less than 20 Dimethindene Maleate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg. of dimethindene maleate, to a 125-ml. separator, suspend the powder in 15 ml. of chloroform, and extract with four 10-ml. portions of 0.1 *N* sulfuric acid. Filter the extracts through a pledget of glass wool washed with 0.1 *N* sulfuric acid into a 50-ml. volumetric flask. Wash the filter with an additional 5 ml. of 0.1 *N* sulfuric acid, and add to the combined extracts. Dilute to volume with 0.1 *N* sulfuric acid, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 0.1 *N* sulfuric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dimethindene Maleate Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 258 mμ, with a suitable spectrophotometer, using 0.1 *N* sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{20}H_{24}N_2 . C_4H_4O_4$ in the portion of Tablets taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Dimethindene Maleate Tablets in well-closed, light-resistant containers.

Tablets available—Dimethindene Maleate Tablets usually available contain the following amount of dimethindene maleate: 1 mg.

CATEGORY and DOSE—See Dimethindene Maleate.

Dimethisoquin Hydrochloride



3-Butyl-1-[2-(dimethylamino)ethoxy]isoquinoline Monohydrochloride

$C_{17}H_{24}N_2O . HCl$ Mol. wt. 308.85

Dimethisoquin Hydrochloride, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_{17}H_{24}N_2O . HCl$.

Description—Dimethisoquin Hydrochloride occurs as a white to off-white, odorless, crystalline powder.

Solubility—Dimethisoquin Hydrochloride is freely soluble in water, in chloroform, and in alcohol. It is very slightly soluble in ether.

Identification—

A: A solution of Dimethisoquin Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 808.

B: To 10 ml. of a solution of Dimethisoquin Hydrochloride add several drops of ammonium reineckate T.S.: a pink precipitate forms.

Melting range, page 814—Dimethisoquin Hydrochloride melts between 144° and 148°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Dimethisoquin Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Dimethisoquin Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—A 1 in 20,000 solution of Dimethisoquin Hydrochloride in isopropyl alcohol exhibits absorbance maxima at 328 ± 2 mμ, 316 ± 2 mμ, and 285 ± 2 mμ, and the ratio A_{316}/A_{328} is between 1.05 and 1.12.

pH, page 824—The pH of a solution of Dimethisoquin Hydrochloride (1 in 100) is between 3.5 and 5.5.

Loss on drying, page 814—Dry Dimethisoquin Hydrochloride at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Dimethisoquin Hydrochloride yields not more than 0.05 percent of residue on ignition.

Assay—Transfer about 100 mg. of Dimethisoquin Hydrochloride, previously dried at 105° for 2 hours and accurately weighed, to a 100-ml. volumetric flask, add isopropyl alcohol to volume, and mix. Pipet 5.0 ml. of this solution into a second 100-ml. volumetric flask, dilute to volume with isopropyl alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dimethisoquin Hydrochloride Reference Standard in isopropyl alcohol, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at 360 mμ and at the maximum at about 328 mμ, with a suitable spectrophotometer, using isopropyl alcohol as the blank. Calculate the quantity, in mg., of $C_{17}H_{24}N_2O.HCl$ in the Dimethisoquin Hydrochloride taken by the formula $2C \times (A_{U328} - A_{U360})/(A_{S328} - A_{S360})$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_{U328} and A_{U360} are the absorbances of the sample solution at 328 mμ and 360 mμ, respectively, and A_{S328} and A_{S360} are the absorbances of the Reference Standard solution at 328 mμ and 360 mμ, respectively.

Packaging and storage—Preserve Dimethisoquin Hydrochloride in well-closed, light-resistant containers.

CATEGORY—Local anesthetic.

APPLICATION—Topically to the skin as a 0.5 percent ointment or lotion two to four times a day.

Dimethisoquin Hydrochloride Lotion

Dimethisoquin Hydrochloride Lotion contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{17}H_{24}N_2O.HCl$.

Identification—The solution from the *Assay* meets the requirement for *Ultraviolet absorption* under *Dimethisoquin Hydrochloride,* page 243.

Assay—Transfer an accurately weighed portion of Dimethisoquin Hydrochloride Lotion, equivalent to about 10 mg. of dimethisoquin hydrochloride, to a 200-ml. volumetric flask. Add about 100 ml. of isopropyl alcohol, shake, then dilute to volume with isopropyl alcohol, and mix. Filter a portion of the mixture, discarding the first 25 to 50 ml. of the filtrate. Concomitantly determine the absorbance of this solution and of a solution of NF Dimethisoquin Hydrochloride Reference Standard in isopropyl alcohol, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at 360 mμ and at the maximum at about 328 mμ, with a suitable spectrophotometer, using isopropyl alcohol as the blank. Calculate the quantity, in mg., of $C_{17}H_{24}N_2O.HCl$ in the portion of the Lotion taken by the formula $0.2C \times (A_{U328} - A_{U360})/(A_{S328} - A_{S360})$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_{U328} and A_{U360} are the absorbances of the sample solution at 328 mμ and 360 mμ, respectively, and A_{S328} and A_{S360} are the absorbances of the Reference Standard solution at 328 mμ and 360 mμ, respectively.

Packaging and storage—Preserve Dimethisoquin Hydrochloride Lotion in tight, light-resistant containers.

Lotion available—Dimethisoquin Hydrochloride Lotion usually available contains 0.5 percent of dimethisoquin hydrochloride.

CATEGORY and APPLICATION—See Dimethisoquin Hydrochloride.

Dimethisoquin Hydrochloride Ointment

Dimethisoquin Hydrochloride Ointment contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{24}N_2O.HCl$.

Identification—The solution from the *Assay* meets the requirement for *Ultraviolet absorption* under *Dimethisoquin Hydrochloride*, page 243.

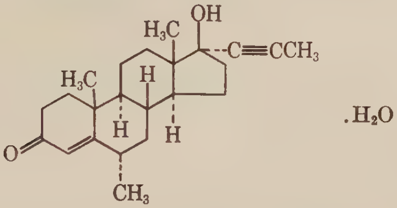
Assay—Transfer an accurately weighed portion of Dimethisoquin Hydrochloride Ointment, equivalent to about 10 mg. of dimethisoquin hydrochloride, to a 200-ml. volumetric flask, and proceed as directed in the *Assay* under *Dimethisoquin Hydrochloride Lotion*, page 244, beginning with "Add about 100 ml. of isopropyl alcohol. . . ." Calculate the quantity, in mg., of $C_{17}H_{24}N_2O.HCl$ in the portion of the Ointment taken by the formula $0.2C \times (A_{U328} - A_{U360})/(A_{S328} - A_{S360})$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_{U328} and A_{U360} are the absorbances of the sample solution at 328 mμ and 360 mμ, respectively, and A_{S328} and A_{S360} are the absorbances of the Reference Standard solution at 328 mμ and 360 mμ, respectively.

Packaging and storage—Preserve Dimethisoquin Hydrochloride Ointment in tight, light-resistant containers.

Ointment available—Dimethisoquin Hydrochloride Ointment usually available contains 0.5 per cent of dimethisoquin hydrochloride.

CATEGORY and APPLICATION—See Dimethisoquin Hydrochloride.

Dimethisterone*



17β-Hydroxy-6α-methyl-17-(1-propynyl)androst-4-en-3-one

$C_{23}H_{32}O_2.H_2O$ Mol. wt. 358.52

Dimethisterone contains not less than 97.0 percent and not more than 103.0 percent of $C_{23}H_{32}O_2.H_2O$.

Description—Dimethisterone occurs as a white crystalline powder. It is odorless and tasteless. When tested by the method for *Class Ia*, page 815, it melts at about 110° with decomposition.

Solubility—Dimethisterone is soluble in alcohol and is slightly soluble in acetone and in chloroform. It is practically insoluble in water.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dimethisterone, previously dried over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Dimethisterone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Dimethisterone in alcohol exhibits maxima and minima at the same wavelengths as that of NF Dimethisterone Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Dimethisterone, calculated on the anhydrous basis, determined in a solution in chloroform containing 200 mg. of Dimethisterone in each 10 ml., is between +16.5° and +21.5° at 20°.

Water, page 900—Determine the water content of Dimethisterone by the titrimetric method: not less than 4.8 percent and not more than 5.7 percent is found.

Residue on ignition, page 858—Dimethisterone yields not more than 0.1 percent of residue on ignition.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Dimethisterone Reference Standard, previously dried over silica gel for 4 hours.

Test preparation—Weigh accurately about 80 mg. of Dimethisterone, previously dried over silica gel for 4 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and ethyl acetate (4:3), and determining the absorbance at the maximum at about 242 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Dimethisterone taken: not more than 3 percent is found.

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* Patented. See notice, page ii.

Assay—Transfer about 50 mg. of Dimethisterone, accurately weighed, to a 50-ml. volumetric flask, add dehydrated alcohol to volume, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with dehydrated alcohol, and mix. Transfer to a second 100-ml. volumetric flask 10.0 ml. of this last solution, dilute to volume with dehydrated alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dimethisterone Reference Standard, previously dried over silica gel for 4 hours, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 242 mμ, with a suitable spectrophotometer, using dehydrated alcohol as the blank. Calculate the quantity, in mg., of $C_{23}H_{32}O_2.H_2O$ in the Dimethisterone taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

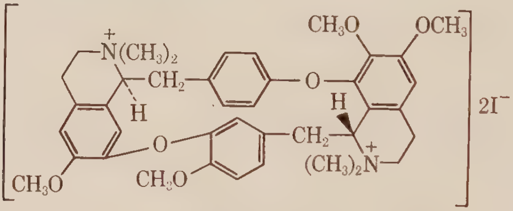
Packaging and storage—Preserve Dimethisterone in tight containers, and avoid excessive heat.

CATEGORY—Progestin.

USUAL DOSE—See Ethinyl Estradiol and Dimethisterone Tablets.

Dimethisterone and Ethinyl Estradiol Tablets, page 293

Dimethyl Tubocurarine Iodide



(+)-*O,O′*-Dimethyltubocurarine Diiodide

$C_{40}H_{48}I_2N_2O_6$ Mol. wt. 906.65

Dimethyl Tubocurarine Iodide, dried in vacuum at 75° for 8 hours, contains not less than 95.0 percent and not more than 105.0 percent of $C_{40}H_{48}I_2N_2O_6$.

Description—Dimethyl Tubocurarine Iodide occurs as an odorless, white or pale yellow crystalline powder.

Solubility—Dimethyl Tubocurarine Iodide is slightly soluble in water, in diluted hydrochloric acid, and in dilute solutions of sodium hydroxide. It is very slightly soluble in alcohol, and practically insoluble in benzene, in chloroform, and in ether.

Identification—

A: Dimethyl Tubocurarine Iodide decomposes with the evolution of gas when heated to about 257°.

B: Dissolve 50 mg. of Dimethyl Tubocurarine Iodide in 30 ml. of water. To 5 ml. of the solution add several drops of nitric acid and 1 ml. of silver nitrate T.S.: a curdy, yellow precipitate forms which is insoluble in ammonia T.S.

C: To another 5-ml. portion of the solution prepared under *Identification test B*, add 1 ml. of ammonium reineckate solution (1 in 25): a pink precipitate forms.

D: To another 5-ml. portion of the solution prepared under *Identification test B*, add about 2 ml. of a saturated solution of picric acid: a yellow precipitate forms.

Loss on drying, page 814—Dry Dimethyl Tubocurarine Iodide in vacuum at 75° for 8 hours: it loses not more than 7 percent of its weight.

Specific rotation, page 822—The specific rotation of Dimethyl Tubocurarine Iodide, calculated on the dried basis, determined in a solution in water containing 25 mg. of Dimethyl Tubocurarine Iodide in each 10 ml., is between +148° and +158°.

Tubocurarine chloride—Dissolve 10 mg. of Dimethyl Tubocurarine Iodide in 6 ml. of water. Add 3 ml. of Folin-Ciocalteu phenol T.S., previously diluted (1 in 4) with water, and adjust the volume to 25 ml. with water. Add 2 ml. of a solution of sodium carbonate (1 in 5) and heat the mixture for 3 minutes in a boiling water bath: the solution is colorless or very faintly blue.

Assay—Weigh accurately about 100 mg. of Dimethyl Tubocurarine Iodide, previously dried in vacuum at 75° for 8 hours, dissolve it in sufficient water to make 100.0 ml., and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, add 0.1 ml. of hydrochloric acid, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dimethyl Tubocurarine Iodide Reference Standard, in the same medium at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 280 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{40}H_{48}I_2N_2O_6$ in the Dimethyl Tubocurarine Iodide taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg., per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Dimethyl Tubocurarine Iodide in tight containers.

Category—Skeletal muscle relaxant.

Usual dose range—Intravenous, initial, **1.5** to **8 mg.** given over a 60-second period. Maintenance, **500 mcg.** to **1 mg.** every 25 to 90 minutes.

Dimethyl Tubocurarine Iodide Injection

Dimethyl Tubocurarine Iodide Injection is a sterile solution of dimethyl tubocurarine iodide in isotonic sodium chloride solution. Each ml. exhibits a potency, in terms of mg. of NF Dimethyl Tubocurarine Iodide Reference Standard, equivalent to not less than 93.0 percent and not more than 107.0 percent of the potency stated on the label.

Identification—Evaporate an amount of Dimethyl Tubocurarine Iodide Injection, equivalent to about 5 mg. of dimethyl tubocurarine iodide, to dryness on a steam bath. Add 5 ml. of water and again evaporate to dryness. Repeat the process with another 5 ml. of water. Dissolve the residue in 10 ml. of water. The solution responds to *Identification tests B, C,* and *D* under *Dimethyl Tubocurarine Iodide,* page 246.

Other requirements—Dimethyl Tubocurarine Iodide Injection meets the requirements under *Injections,* page 810.

Assay—

Standard solution—Dissolve NF Dimethyl Tubocurarine Iodide Reference Standard in sufficient water to make a solution having a final concentration of 50.0 mcg. per ml. Preserve in a cold place in a tight container, and use it within 90 days after preparation.

The rabbits—Use healthy rabbits which have been maintained without loss of weight for at least 1 week on a uniform, unrestricted diet and which weigh between 1.5 and 4.0 kg., except that in any one assay the weight of the heaviest rabbit shall be not more than twice that of the lightest rabbit. If the rabbits have not been used for this assay within the previous 7 days, condition them by the injection of one head-drop dose of the *Standard solution* in accordance with directions given below, on at least two different days during the preceding week. Use the animals daily if desired, but do not use them more than once each day.

Procedure—Divide the rabbits into two equal groups of at least eight each. Suitably restrain them in a prone position with the head free, taking precautions to prevent struggling. Place the *Standard solution* in a small-bore buret joined with flexible tubing to a hypodermic needle inserted in a marginal ear vein, and inject a 0.1-ml. dose of the solution every 15 seconds into each rabbit of the first group until head-drop occurs. Replace any rabbit which struggles vigorously during the injection. Consider that head-drop is complete if the rabbit, in response to a light tap on the back, is incapable of raising its head when it has fallen forward or of righting its head when laid on one cheek by the operator. Record the number of doses injected. In a similar manner, inject each rabbit of the second group with Dimethyl Tubocurarine Iodide Injection diluted with water to give approximately the same concentration as the *Standard solution.* Record the number of doses injected.

Repeat the procedure on the following day but inject the *Standard solution* into the group which previously received the Injection and vice versa.

Calculation of the potency—For each rabbit which received both the *Standard solution* and the Dimethyl Tubocurarine Iodide Injection, divide the number of doses injected of the *Standard solution* by the number of doses injected of the Injection. Find the logarithm of each quotient so obtained and calculate the average (L) of these logarithms. The potency expressed in mg. of dimethyl tubocurarine iodide (as represented by

NF Dimethyl Tubocurarine Iodide Reference Standard) per ml., is given by the formula:

$$\text{Potency} = \frac{0.05 \times \text{antilog } L}{\text{Volume of Injection in each ml. of diluted Injection}}$$

For the group of rabbits which first received the *Standard solution* subtract the smallest value of the logarithm from the largest value, thus obtaining R_1, the range. In a similar manner, obtain the value R_2, the range in the logarithms for the group which received the Injection first, and calculate the standard error of the assay by the following formula:

$$\text{Standard error of the Assay} = c \times \text{potency} \times (R_1 + R_2)$$

in which c has a value determined by N, the total number of rabbits which received both the *Standard solution* and the Injection, as follows:

N	14	16	18	20
c	.114	.101	.091	.084
N	22	24	26	28
c	.077	.072	.068	.064

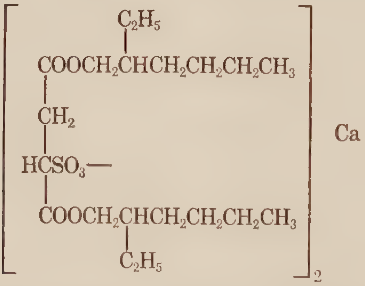
If the standard error exceeds 2.5 percent of the labeled potency, repeat the assay or use more rabbits until the standard error of the combined result is not more than 2.5 percent.

Packaging and storage—Preserve Dimethyl Tubocurarine Iodide Injection in single-dose or multiple-dose containers, preferably of Type I glass. Phenol, 0.5 percent, or some other suitable bacteriostatic substance, must be added to the Injection in multiple-dose containers.

Injections available—Dimethyl Tubocurarine Iodide Injection usually available contains the following amounts of dimethyl tubocurarine iodide: 5 mg. in 10 ml., 10 mg. in 10 ml., 40 mg. in 20 ml., and 50 mg. in 50 ml.

CATEGORY and DOSE—See Dimethyl Tubocurarine Iodide.

Dioctyl Calcium Sulfosuccinate*



Bis(2-ethylhexyl) *S*-Calcium Sulfosuccinate

$C_{40}H_{74}CaO_{14}S_2$ Mol. wt. 883.24

Dioctyl Calcium Sulfosuccinate contains not less than 91.0 percent and not more than 100.5 percent of $C_{40}H_{74}CaO_{14}S_2$, calculated on the dried basis.

Description—Dioctyl Calcium Sulfosuccinate occurs as a white, gelatinous solid having the characteristic odor of octyl alcohol. It is free of the odor of other solvents.

Solubility—Dioctyl Calcium Sulfosuccinate is slightly soluble in water. It is freely soluble in alcohol and glycerin, and is very soluble in polyethylene glycol 400 and in corn oil.

Clarity of solution—Dissolve 25 g. of Dioctyl Calcium Sulfosuccinate in 94 ml. of alcohol: the solution does not develop a haze within 24 hours.

Loss on drying, page 814—Dry Dioctyl Calcium Sulfosuccinate at 105° for 2 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Dioctyl Calcium Sulfosuccinate yields not less than 14.0 percent and not more than 16.0 percent of residue on ignition, calculated on the anhydrous basis.

Arsenic—A *Test preparation* prepared with 5 g. of Dioctyl Calcium Sulfosuccinate, as directed for organic compounds, meets the requirements of the *Arsenic Test,* page 777 (2 parts per million As).

Heavy metals, page 806—Transfer

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* Patented. See notice, page ii.

2.0 g. of Dioctyl Calcium Sulfosuccinate to a platinum crucible, and ignite until free from carbon. Cool, moisten the residue obtained with 1 ml. of hydrochloric acid, and evaporate to dryness on a steam bath. Add 2 ml. of diluted acetic acid, digest on a steam bath for 5 minutes, filter into one of a pair of matched 50-ml. color-comparison tubes, and wash the residue with sufficient water to make 25 ml.: the heavy metals limit for Dioctyl Calcium Sulfosuccinate is 10 parts per million.

Assay—

Assay preparation—Transfer 3.000 g. of Dioctyl Calcium Sulfosuccinate to a 400-ml. beaker. Add 50 ml. of hot water, and stir until a paste is formed. Add two additional 50-ml. portions of hot water, and stir until the sample is completely dissolved. [Note—Dioctyl Calcium Sulfosuccinate dissolves slowly in water, and solution must be complete at this point.] Cool the solution to room temperature, transfer it quantitatively, with the aid of water, to a 1000-ml. volumetric flask, dilute to volume with water, and mix.

Tetra-n-butylammonium iodide solution—Transfer 1.250 g. of tetra-*n*-butylammonium iodide to a 500-ml. volumetric flask, dilute to volume with water, and mix.

Salt solution—Transfer 100 g. of anhydrous sodium sulfate and 10 g. of sodium carbonate to a 400-ml. beaker, and add sufficient water to dissolve the two salts. Transfer the solution to a 1000-ml. volumetric flask, dilute to volume, and mix.

Procedure—Pipet 25.0 ml. of *Tetra-n-butylammonium iodide solution* into a 250-ml. conical flask. Transfer 50 ml. of the *Salt solution*, 25 ml. of chloroform, and 0.4 ml. of bromophenol blue T.S. to the flask. Stopper, and shake vigorously for 20 to 30 seconds or until all of the blue color goes into the lower chloroform layer. Titrate the solution with the *Assay preparation*, until about 1 ml. from the end-point, and shake the stoppered flask vigorously for about 2 minutes. Continue the titration in 2-drop increments, shaking the stoppered flask vigorously for about 10 seconds after each addition, and then allow the flask to stand about 10 seconds or until the chloroform layer has separated. Continue the titration until the blue color is completely absent in the chloroform layer. Calculate the percent of Dioctyl Calcium Sulfosuccinate by the formula $2490/V$, in which V is the number of ml. of the *Assay preparation* required to reach the end-point, and 2490 is a factor derived by the expression $[1.250 \times (25/500) \times (883.24/2 \times 369.4) \times 100] / [3.000/1000]$.

Packaging and storage—Preserve Dioctyl Calcium Sulfosuccinate in well-closed containers.

Category—Wetting agent; nonlaxative fecal matter softener.

Usual dose—**240 mg.**

Dioctyl Calcium Sulfosuccinate Capsules

Dioctyl Calcium Sulfosuccinate Capsules contain not less than 85.0 percent and not more than 115.0 percent of the labeled amount of $C_{40}H_{74}CaO_{14}S_2$.

Identification—Ash the contents of one Dioctyl Calcium Sulfosuccinate Capsule, dissolve the residue in 10 ml. of 1 *N* hydrochloric acid, and filter: the filtrate responds to the tests for *Calcium*, page 808.

Weight variation, page 901—Dioctyl Calcium Sulfosuccinate Capsules meet the requirements of the weight variation test for capsules, using chloroform as the solvent in the procedure for *Soft capsules*.

Assay—

Tetra-n-butylammonium iodide solution and *Salt solution*—Prepare as directed in the *Assay* under *Dioctyl Calcium Sulfosuccinate*, page 248.

Assay preparation—Cut in half 10 Dioctyl Calcium Sulfosuccinate Capsules, and transfer the capsule halves to a 100-ml. beaker. Rinse the cutting tool with chloroform, collecting the washings in the beaker. To the beaker add about 40 ml. of chloroform, stir for about 30 minutes, and decant the chloroform into a 100-ml. volumetric flask. Rinse the capsule shells and the beaker with several small portions of chloroform, adding the rinsings to the flask. Dilute to volume with chloroform, and mix.

Procedure—Transfer an accurately measured volume of the *Assay preparation*, equivalent to about 50 mg. of dioctyl calcium sulfosuccinate, to a 250-ml. glass-stoppered conical flask. Add chloroform, if necessary, to make 10 ml., and then add to the flask 50 ml. of *Salt solution* and 0.2 ml. of bromophenol blue T.S. Mix, and titrate with *Tetra-n-butylammonium iodide solution* until about 1 ml. from the end-point, and shake the stoppered flask vigorously for about 2 minutes. Continue the titration in 2-drop increments, shaking vigorously for about 10 seconds after each addition, and then allow the flask to stand about 10 seconds or until the chloroform layer has separated. Continue the titration until the chloroform layer assumes a blue color. Each ml. of *Tetra-n-butylammonium iodide solution* is equivalent to 2.989 mg. of $C_{40}H_{74}CaO_{14}S_2$.

Packaging and storage—Preserve Dioctyl Calcium Sulfosuccinate Capsules in tight containers, and store in a cool, dry place.

Capsules available—Dioctyl Calcium Sulfosuccinate Capsules usually available contain the following amounts of dioctyl calcium sulfosuccinate: 50 and 240 mg.

CATEGORY and DOSE—See Dioctyl Calcium Sulfosuccinate.

Dioctyl Sodium Sulfosuccinate Solution*

Dioctyl Sodium Sulfosuccinate Solution contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{20}H_{37}NaO_7S$.

Description—Dioctyl Sodium Sulfosuccinate Solution is a clear liquid having a bitter taste and a faint, characteristic odor. It is colorless unless a color has been added.

Identification—Evaporate to dryness on a steam bath a volume of Dioctyl Sodium Sulfosuccinate Solution equivalent to about 50 mg. of dioctyl sodium sulfosuccinate. Dry the residue at 105° for 30 minutes, cool, and dissolve the residue in 10 ml. of chloroform. The infrared absorption spectrum of this solution exhibits maxima at the same wavelengths as that of USP Dioctyl Sodium Sulfosuccinate Reference Standard, similarly measured.

pH, page 824—The pH of Dioctyl Sodium Sulfosuccinate Solution is between 5.8 and 6.9.

Assay—

Assay preparation—Transfer an accurately measured volume of Dioctyl Sodium Sulfosuccinate Solution, equivalent to about 300 mg. of dioctyl sodium sulfosuccinate, to a 100 ml. volumetric flask, dilute to volume with water, and mix.

Tetra-n-butylammonium iodide solution—Transfer 1.250 g. of tetra-*n*-butylammonium iodide to a 500-ml. volumetric flask. Dilute to volume with water, and mix.

Salt solution—Transfer 100 g. of anhydrous sodium sulfate and 10 g. of sodium carbonate to a 1000-ml. volumetric flask, add sufficient water to dissolve the two salts, dilute to volume with water, and mix.

Procedure—Pipet 25.0 ml. of *Tetra-n-butylammonium iodide solution* into a 250-ml. conical flask. Transfer 50.0 ml. of the *Salt solution*, 25 ml. of chloroform, and 0.4 ml. of bromophenol blue T.S. to the flask. Stopper and shake vigorously for 20 to 30 seconds or until all of the blue color goes into the lower chloroform layer. Titrate the *Tetra-n-butylammonium iodide solution* with the *Assay preparation*, using a 50-ml. buret, until about 1 ml. from the end-point, and shake the stoppered flask vigorously for about 2 minutes. Continue the titration in 2-drop increments, shaking the stoppered flask vigorously for about 10 seconds after each addition, and then allow the flask to stand about 10 seconds or until the chloroform layer has separated. Continue the titration until the blue color is completely absent in the chloroform layer. Calculate the quantity, in mg., of $C_{20}H_{37}NaO_7S$ in each ml. of the Solution taken by the formula $7522/vV$, in which v is the volume, in ml., of the Solution taken, V is the volume, in ml., of the *Assay preparation* required to reach the end-point, and 7522 is a factor derived by the expression $[1250 \times (26/500) \times (444.6/369.4) \times 100]$.

Packaging and storage—Preserve Dioctyl Sodium Sulfosuccinate Solution in tight containers.

Solution available—Dioctyl Sodium Sulfosuccinate Solution usually available contains the following amount of dioctyl sodium sulfosuccinate: 10 mg. in 1 ml.

CATEGORY—Fecal matter softener.

USUAL DOSE RANGE OF DIOCTYL SODIUM SULFOSUCCINATE—**50 to 200 mg.**

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* Patented. See notice, page ii.

Dioctyl Sodium Sulfosuccinate Syrup

Dioctyl Sodium Sulfosuccinate Syrup contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{20}H_{37}NaO_7S$.

Identification—

Tetra-n-butylammonium iodide solution and *Salt solution*—Prepare as directed in the *Assay* under *Dioctyl Sodium Sulfosuccinate Solution*, page 250.

Procedure—Place 100 ml. of *Salt solution* and 50 ml. of chloroform in a 250-ml. glass-stoppered cylinder, add 6 drops of bromophenol blue T.S. and 0.7 ml. of *Tetra-n-butylammonium iodide solution*, and mix for 10 seconds. The blue indicator is transferred to the chloroform layer. Slowly add a volume of Dioctyl Sodium Sulfosuccinate Syrup, equivalent to about 40 mg. of dioctyl sodium sulfosuccinate, to the cylinder, and then shake for 30 seconds: the indicator migrates to the aqueous layer, giving it a violet color.

pH, page 824—The pH of Dioctyl Sodium Sulfosuccinate Syrup is between 5.5 and 6.5.

Assay—

Standard preparation—Transfer about 100 mg. of USP Dioctyl Sodium Sulfosuccinate Reference Standard, previously dried at 105° for 2 hours and accurately weighed, to a 100-ml. volumetric flask, dissolve in 2.5 ml. of alcohol, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a 1000-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer an accurately measured volume of Dioctyl Sodium Sulfosuccinate Syrup, equivalent to about 100 mg. of dioctyl sodium sulfosuccinate, to a 1000-ml. volumetric flask, allowing the pipet to drain for 15 minutes. Dilute to volume with water, and mix. Transfer 10.0 ml. of the solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Transfer 20.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate separators, and transfer 20 ml. of water to a third separator to serve as the blank. To each separator add 5 drops of hydrochloric acid, mix by swirling, add 1.0 ml. of methylene blue solution (1 in 1000), and mix by swirling. To each separator add 20.0 ml. of chloroform, and shake vigorously for 5 minutes. Wash each chloroform solution, in clean separators, with 20 ml. of water, shaking vigorously for 60 seconds. Discard the washings, and filter each chloroform solution through cotton into a 100-ml. volumetric flask, washing each separator with two 10-ml. portions of chloroform and filtering the washings into each flask. Dilute each flask to volume with chloroform, and mix. Concomitantly determine the absorbance of the solutions, in 1-cm. cells, at the maximum at about 650 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{20}H_{37}NaO_7S$ in each ml. of the Syrup taken by the formula $10 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Syrup taken.

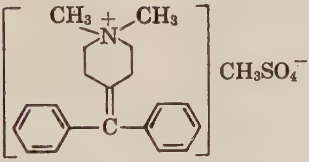
Packaging and storage—Preserve Dioctyl Sodium Sulfosuccinate Syrup in tight, light-resistant containers.

Syrup available—Dioctyl Sodium Sulfosuccinate Syrup usually available contains the following amount of dioctyl sodium sulfosuccinate: 20 mg. in 5 ml.

Category—Fecal matter softener.

Usual dose of dioctyl sodium sulfosuccinate—**50** to **200 mg.**

Diphemanil Methylsulfate*



4-(Diphenylmethylene)-1,1-dimethylpiperidinium Methyl Sulfate

$C_{21}H_{27}NO_4S$ Mol. wt. 389.52

Diphemanil Methylsulfate contains not less than 97.0 percent and not more than 103.0 percent of $C_{21}H_{27}NO_4S$, calculated on the dried basis.

Description—Diphemanil Methylsulfate occurs as a white or nearly white, crystalline solid, possessing a bitter taste, and a faint characteristic odor. It is stable to heat and to light, and is somewhat hygroscopic.

Solubility—Diphemanil Methylsulfate is sparingly soluble in water, in alcohol, and in chloroform.

Identification—Prepare a solution of Diphemanil Methylsulfate in methanol containing 1 mg. per ml. On a line parallel to and not more than 2 cm. from the edge of a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 10 µl. of this solution and 10 µl. of a methanol solution of NF Diphemanil Methylsulfate Reference Standard containing 1 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of hydrochloric acid and methoxyethanol (1:100) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under shortwave ultraviolet light: the R_f value of the main spot obtained from the sample corresponds to that obtained with the Reference Standard.

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* Patented. See notice, page ii.

Melting range, page 814—Diphemanil Methylsulfate melts between 189° and 196°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Diphemanil Methylsulfate, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Diphemanil Methylsulfate Reference Standard, similarly measured.

pH, page 824—The pH of a solution of Diphemanil Methylsulfate (1 in 100) is between 4.0 and 6.0.

Loss on drying, page 814—Dry Diphemanil Methylsulfate at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Diphemanil Methylsulfate yields not more than 0.1 percent of residue on ignition. Retain the residue from a 1-g. sample for the *Heavy metals test.*

Heavy metals, page 806—Dissolve the residue resulting from the *Residue on ignition test* in 23 ml. of water and add 2 ml. of diluted acetic acid: the heavy metals limit for Diphemanil Methylsulfate is 20 parts per million.

Assay—

Buffer solution—Dissolve 9.23 g. of Na_2HPO_4 in 800 ml. of water, adjust to pH 4 with saturated citric acid solution, dilute to 1000.0 ml. with water, and mix.

Standard preparation—Dissolve about 50 mg. of NF Diphemanil Methylsulfate Reference Standard, accurately weighed, in sufficient water to make 500.0 ml., and mix.

Assay preparation—Dissolve about 50 mg. of Diphemanil Methylsulfate, accurately weighed, in sufficient water to make 500.0 ml., and mix.

Procedure—Treat the standard and the sample solutions and the blank similarly and concurrently. Transfer 10.0 ml. each of the *Standard preparation* and the *Assay preparation* and of *Buffer solution* to separate 250-ml. separators, add to each 40 ml. of *Buffer solution*, 10 ml. of a solution of bromophenol blue in chloroform (1 in 1000), and 60 ml. of chloroform. Shake the separators vigorously for 2 minutes, let stand for 15 minutes, then withdraw the chloroform layers through chloroform-washed cotton into 100-ml. volumetric flasks. Repeat the extraction with 20 ml. of chloroform, adding the filtered chloroform extracts to the respective volumetric flasks, dilute to volume with chloroform, and mix. Without delay, concomitantly determine the absorbance of the solutions in 1-cm. cells, at the maximum at about 412 mµ with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{27}NO_4S$ in the portion of Diphemanil Methylsulfate taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Diphemanil Methylsulfate in tight containers.

CATEGORY—Anticholinergic.

USUAL DOSE—Oral, **100 mg.** every 4 to 6 hours. Intramuscular and subcutaneous, **25 mg.** four times a day.

USUAL DOSE RANGE—Oral, **50** to **200 mg.**

Diphemanil Methylsulfate Injection

Diphemanil Methylsulfate Injection is a sterile solution of diphemanil methylsulfate in a suitable aqueous vehicle. It contains not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $C_{21}H_{27}NO_4S$.

Identification—Dilute Diphemanil Methylsulfate Injection with methanol to obtain a solution containing about 1 mg. per ml. Proceed as directed in the *Identification test* under *Diphemanil Methylsulfate*, page 251, beginning with "On a line parallel to . . . ."

pH, page 824—The pH of Diphemanil Methylsulfate Injection is between 3.0 and 5.0.

Other requirements—Diphemanil Methylsulfate Injection meets the requirements under *Injections*, page 810.

Assay—

Buffer solution—Prepare as directed in the *Assay* under *Diphemanil Methylsulfate*, page 251.

Standard preparation—Prepare as directed in the *Assay* under *Diphemanil Methylsulfate*, page 251.

Assay preparation—Transfer an accurately measured volume of Diphemanil Methylsulfate Injection, equivalent to about 50 mg. of diphemanil methylsulfate, to a 500-ml. volumetric flask, add water to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Diphemanil Methylsulfate*, page 251. Calculate the quantity, in mg., of $C_{21}H_{27}NO_4S$ in each ml. of the Injection taken by the formula $0.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration of the *Standard preparation*, in mcg. per ml., V is the volume, in ml., of the Injection taken, A_U is the absorbance of the solution from the *Sample preparation*, and A_S is the absorbance of the solution from the *Standard preparation*.

Packaging and storage—Preserve Diphemanil Methylsulfate Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Diphemanil Methylsulfate Injection usually available contains the following amounts of diphemanil methylsulfate: 25 mg. in 1 ml., and 250 mg. in 10 ml.

CATEGORY and DOSE—See Diphemanil Methylsulfate.

Diphemanil Methylsulfate Tablets

Diphemanil Methylsulfate Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $C_{21}H_{27}NO_4S$.

Identification—Shake a quantity of finely powdered Diphemanil Methylsulfate Tablets, equivalent to about 25 mg. of diphemanil methylsulfate, with 25 ml. of methanol for 15 minutes, and filter. Proceed as directed in the *Identification test* under *Diphemanil Methylsulfate*, page 251, beginning with "On a line parallel to . . . ."

Disintegration, page 878—The disintegration time limit for Diphemanil Methylsulfate Tablets is 10 minutes.

Weight variation, page 901—Diphemanil Methylsulfate Tablets meet the requirements of the weight variation test for tablets.

Assay—

Buffer solution—Prepare as directed in the *Assay* under *Diphemanil Methylsulfate*, page 251.

Standard preparation—Prepare as directed in the *Assay* under *Diphemanil Methylsulfate*, page 251.

Assay preparation—Weigh and finely powder not less than 10 Diphemanil Methylsulfate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of diphemanil methylsulfate, in a 500-ml. volumetric flask, add 150 ml. of water, shake mechanically for 15 minutes, add water to volume, mix, and filter through a dry filter, discarding the first 25 ml. of filtrate.

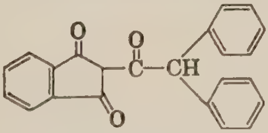
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Diphemanil Methylsulfate*, page 251. Calculate the quantity, in mg., of $C_{21}H_{27}NO_4S$ in the portion of the Tablets taken by the formula $0.5\,C \times (A_U/A_S)$, in which C is the exact concentration of the *Standard preparation*, in mcg. per ml., A_U is the absorbance of the solution from the *Assay preparation*, and A_S is the absorbance of the solution from the *Standard preparation*.

Packaging and storage—Preserve Diphemanil Methylsulfate Tablets in tight containers.

Tablets available—Diphemanil Methylsulfate Tablets usually available contain the following amount of diphemanil methylsulfate: 100 mg.

CATEGORY and DOSE—See Diphemanil Methylsulfate.

Diphenadione*



2-(Diphenylacetyl)-1,3-indandione

$C_{23}H_{16}O_3$ Mol. wt. 340.38

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* Patented. See notice, page ii.

Diphenadione contains not less than 98.0 percent and not more than 100.5 percent of $C_{23}H_{16}O_3$, calculated on the dried basis.

Description—Diphenadione occurs as yellow crystals or as a yellow, crystalline powder. It is odorless.

Solubility—Diphenadione is practically insoluble in water. It is soluble in benzene, in ether, and in glacial acetic acid. It is slightly soluble in acetone and in alcohol.

Identification—

A: To a saturated solution of Diphenadione in 0.01 *N* sodium hydroxide add an equal volume of 10 *N* sodium hydroxide: a yellow precipitate is formed.

B: Dissolve 50 mg. of Diphenadione in 1.5 ml. of alcohol and add 1 drop of ferric chloride T.S.: a brick-red suspension is formed.

Melting range, page 814—Diphenadione melts between 144° and 150°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Diphenadione, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Diphenadione Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Diphenadione in a mixture of one volume of 0.1 *N* sulfuric acid and 19 volumes of alcohol exhibits maxima and minima at the same wavelengths as that of NF Diphenadione Reference Standard, similarly measured.

Loss on drying, page 814—Dry Diphenadione at 105° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Diphenadione yields not more than 0.1 percent of residue on ignition.

Assay—Transfer to a 100-ml. volumetric flask about 50 mg. of Diphenadione, accurately weighed, add a mixture of one volume of 0.1 *N* sulfuric acid and 19 volumes of alcohol to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with the alcoholic sulfuric acid, and mix. Transfer to a third 100-ml. volumetric flask 10.0 ml. of this last solution, dilute to volume with the alcoholic sulfuric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Diphenadione Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 289 mμ, with a suitable spectrophotometer, using the alcoholic sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{23}H_{16}O_3$ in the Diphenadione taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Diphenadione in tight, light-resistant containers.

CATEGORY—Anticoagulant.

USUAL DOSE—Initial, **20** to **30 mg.** the first day, **10** to **15 mg.** the second day. Maintenance, **2.5** to **5 mg.** daily.

USUAL DOSE RANGE—**2.5** to **30 mg.**

Diphenadione Tablets

Diphenadione Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{23}H_{16}O_3$.

Identification—Digest with 50 ml. of benzene for 15 minutes an amount of powdered Diphenadione Tablets, equivalent to about 20 mg. of diphenadione. Filter the mixture and evaporate the filtrate to dryness on a steam bath: the diphenadione thus obtained meets the requirement for *Infrared absorption* under *Diphenadione*, page 253.

Disintegration, page 878—The disintegration time limit for Diphenadione Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Diphenadione Tablets meet the requirements of the content uniformity test for tablets.

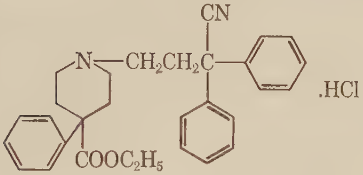
Assay—Weigh and finely powder not less than 10 Diphenadione Tablets. Weigh accurately a portion of the powder equivalent to about 5 mg. of diphenadione, and transfer completely, with the aid of 15 ml. of water, to a separator. Extract the diphenadione completely, using four 20-ml. portions of chloroform, filtering each portion through chloroform-washed cotton into a 100-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 10.0 ml. of this solution into a 100-ml. volumetric flask and evaporate the chloroform on a steam bath just to dryness. Dissolve the residue in 25 ml. of 0.005 *N* sulfuric acid in alcohol, warming on a steam bath to ensure complete solution of the diphenadione, and cool to room temperature. Add alcoholic sulfuric acid to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Diphenadione Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 289 mμ, with a suitable spectrophotometer, using the alcoholic sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{23}H_{16}O_3$ in the portion of the Tablets taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Diphenadione Tablets in tight containers.

Tablets available—Diphenadione Tablets usually available contain the following amount of diphenadione: 5 mg.

CATEGORY and DOSE—See Diphenadione.

Diphenoxylate Hydrochloride*



Ethyl 1-(3-Cyano-3,3-diphenylpropyl)-4-phenylisonipecotate Hydrochloride

$C_{30}H_{32}N_2O_2 . HCl$ Mol. wt. 489.06

Diphenoxylate Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{30}H_{32}N_2O_2 . HCl$, calculated on the dried basis.

Description—Diphenoxylate Hydrochloride occurs as a white, odorless, crystalline powder. A saturated solution has a pH of about 3.3.

Solubility—Diphenoxylate Hydrochloride is slightly soluble in water and in isopropanol, soluble in methanol, sparingly soluble in alcohol and acetone, and freely soluble in chloroform. It is practically insoluble in ether and in solvent hexane.

Identification—A solution of Diphenoxylate Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 808.

Melting range, page 814—Diphenoxylate Hydrochloride melts between 220° and 226°.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 10 solution of Diphenoxylate Hydrochloride in chloroform, determined in a 0.2-mm. cell, exhibits maxima at the following wavelengths, stated in μ: 3.24 (*sh*), 3.33 (*s*), 4.30 (*vs bd*), 5.76 (*v s*), 6.23 (*m*), 6.28 (*sh*), 6.64 (*s*), 6.76 (*sh*), 6.85 (*s*), 6.96 (*sh*), 7.08 (*m*), 7.22 (*m*), 7.61 (*m bd*), 8.48 (*m*), 8.60 (*w*), 8.73 (*s*), 8.93 (*w bd*), 9.12 (*sh*), 9.24 (*m*), 9.54 (*sh*), 9.77 (*m*), 9.98 (*m bd*), 10.17 (*m*), 10.54 (*w bd*), 10.90 (*m bd*), 11.30 (*v w bd*), 11.60 (*m bd*), 11.96 (*w bd*).

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2000 solution of Diphenoxylate Hydrochloride in 0.01 N methanolic hydrochloric acid exhibits maxima at 252 ± 2 mμ, 257 ± 2 mμ, and at 264 ± 2 mμ. The ratio A_{257}/A_{252} is 1.2 ± 0.1.

Loss on drying, page 814—Dry Diphenoxylate Hydrochloride at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Assay—Dissolve about 300 mg. of Diphenoxylate Hydrochloride, accurately weighed, in 75 ml. of glacial acetic acid, add 4 ml. of mercuric acetate T.S., and titrate with 0.1 N perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Each ml. of 0.1 N perchloric acid is equivalent to 48.91 mg. of $C_{30}H_{32}N_2O_2 . HCl$.

Packaging and storage—Preserve Diphenoxylate Hydrochloride in well-closed containers.

CATEGORY—Antidiarrheal (narcotic).

USUAL DOSE—**5 mg.** four times a day.

USUAL DOSE RANGE—**5** to **40 mg.** per day.

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* Patented. See notice, page ii.

Diphenoxylate Hydrochloride and Atropine Sulfate Solution

Diphenoxylate Hydrochloride and Atropine Sulfate Solution contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{30}H_{32}N_2O_2 . HCl$ (diphenoxylate hydrochloride), and not less than 80.0 percent and not more than 120.0 percent of the labeled amount of $(C_{17}H_{23}NO_3)_2 . H_2SO_4 . H_2O$ (atropine sulfate).

Identification—Transfer a volume of Diphenoxylate Hydrochloride and Atropine Sulfate Solution, equivalent to about 100 mg. of diphenoxylate hydrochloride, to a separator, add 1 ml. of diluted hydrochloric acid and sufficient water to make about 100 ml., and continue as directed for *Identification test A* under *Diphenoxylate Hydrochloride and Atropine Sulfate Tablets*, page 257.

pH, page 824—The pH of Diphenoxylate Hydrochloride and Atropine Sulfate Solution diluted with an equal volume of water is between 3.0 and 3.7.

Assay for diphenoxylate hydrochloride—Transfer an accurately measured volume of Diphenoxylate Hydrochloride and Atropine Sulfate Solution, equivalent to about 100 mg. of diphenoxylate hydrochloride, to a separator, add 4 ml. of diluted hydrochloric acid, and extract with six 30-ml. portions of chloroform. Wash the combined chloroform extracts with 25 ml. of water, and discard the washing. Transfer the chloroform to a beaker, and evaporate nearly to dryness. Add 100 ml. of glacial acetic acid and 4 ml. of mercuric acetate T.S. to the beaker, and titrate with 0.05 *N* perchloric acid in dioxane, determining the end-point potentiometrically. Each ml. of 0.05 *N* perchloric acid is equivalent to 24.45 mg. of $C_{30}H_{32}N_2O_2 . HCl$.

Assay for atropine sulfate—

p-Dimethylaminobenzaldehyde solution—Just prior to use, dissolve 1 g. of *p*-dimethylaminobenzaldehyde in 6 ml. of a cooled mixture of 88 volumes of sulfuric acid and 12 volumes of water.

Standard stock solution—Transfer about 50 mg. of USP Atropine Sulfate Reference Standard, accurately weighed, to a 200-ml. volumetric flask, add 0.1 *N* sulfuric acid to volume, and mix.

Diluted standard preparation—Transfer 2.0 ml. of the *Standard stock solution* to a 250-ml. separator, and continue as directed under *Assay preparation*, beginning with "... and add water to make about 150 ml."

Assay preparation—Transfer an accurately measured volume of Diphenoxylate Hydrochloride and Atropine Sulfate Solution, equivalent to about 500 mcg. of atropine sulfate, to a 250-ml. separator, and add water to make about 150 ml. Make the solution alkaline with ammonia T.S., and extract with six 30-ml. portions of chloroform. Wash the combined chloroform extracts with 25 ml. of water, and discard the washing. Extract the washed chloroform with two 25-ml. portions of 0.1 *N* sulfuric acid, discard the chloroform, and wash the combined acid extracts with 10 ml. of chloroform, discarding the washing. Make the solution alkaline with ammonia T.S., and extract with five 25-ml. portions of chloroform, discarding the aqueous phase. Wash the combined chloroform extracts with 20 ml. of water, and discard the washing. Transfer the chloroform to a 150-ml. beaker, and evaporate to a volume of about 2 ml. Transfer the residual liquid with the aid of chloroform to a 10-ml. volumetric flask, dilute to volume with chloroform, and mix.

Procedure—Transfer 2.0 ml. each of the *Diluted Standard preparation*, the *Assay preparation*, and of chloroform to serve as the blank to separate 250-mm. test tubes, to each tube add a small boiling stone, and evaporate to dryness in a boiling water bath. Dry at 80° for 30 minutes. To each tube add exactly 0.5 ml. of the *p-Dimethylaminobenzaldehyde solution*, and allow to stand, with intermittent rotation of each tube for 2 minutes. Immerse the tubes in a water bath at 70°, and heat for 6 minutes, mixing each tube intermittently without removal from the water bath. Cool in cold water for 3 minutes, then carefully add 5.0 ml. of acetic anhydride to each tube, mix, and allow to stand for 15 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 515 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Diluted standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mcg., of $(C_{17}H_{23}NO_3)_2 . H_2SO_4 . H_2O$ in each ml. of the Solution taken by the formula $10 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Diluted standard preparation*, and V is the volume, in ml., of the Solution taken.

Packaging and storage—Preserve Diphenoxylate Hydrochloride and Atropine Sulfate Solution in tight, light-resistant containers.

Solution available—Diphenoxylate Hydrochloride and Atropine Sulfate Solution usually available contains the following amount of diphenoxylate hydrochloride: 2.5 mg. in 5 ml.; and of atropine sulfate: 25 mcg. in 5 ml.

CATEGORY and DOSE—See Diphenoxylate Hydrochloride.

Diphenoxylate Hydrochloride and Atropine Sulfate Tablets

Diphenoxylate Hydrochloride and Atropine Sulfate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{30}H_{32}N_2O_2 . HCl$ (diphenoxylate hydrochloride), and not less than 80.0 percent and not more than 120.0 percent of the labeled amount of $(C_{17}H_{23}NO_3)_2 . H_2SO_4 . H_2O$ (atropine sulfate).

Identification—Transfer an amount of finely powdered Diphenoxylate Hydrochloride and Atropine Sulfate Tablets, equivalent to about 100 mg. of diphenoxylate hydrochloride, to a separator, add 100 ml. of water and 1 ml. of diluted hydrochloric acid, and extract with five 25-ml. portions of a 9:1 mixture of chloroform and isopropanol. After each extraction transfer the bottom chloroform layer to a second separator, filtering each portion through a sintered-glass filter. Wash the combined chloroform solutions with two 25-ml. portions of water, discard the washings, and evaporate the chloroform to dryness on a steam bath. To the residue add 10 ml. of ether previously saturated with hydrochloric acid, carefully evaporate to dryness, then add a second portion of the acid-saturated ether, and again evaporate to dryness. Slurry the residue with *n*-hexane, allow the solids to settle, and carefully decant off the supernatant liquid. Dry the solids at 105° for 1 hour: the diphenoxylate hydrochloride so obtained responds to the *Infrared absorption test* under *Diphenoxylate Hydrochloride*, page 255, and the ultraviolet absorption spectrum of a 1 in 2000 solution of the residue in 0.01 *N* methanolic hydrochloric acid exhibits maxima at the same wavelengths as that of NF Diphenoxylate Hydrochloride, similarly measured.

Disintegration, page 878—The disintegration time limit for Diphenoxylate Hydrochloride and Atropine Sulfate Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Diphenoxylate Hydrochloride and Atropine Sulfate Tablets meet the requirements of the content uniformity test for tablets, when tested for diphenoxylate content using the following special procedure: Place a tablet in a 50-ml. glass-stoppered centrifuge tube, add an accurately measured volume of methanol to produce a concentration of about 250 mcg. of diphenoxylate hydrochloride per ml., and crush the tablet with a glass rod. Mix by shaking vigorously, and then centrifuge at 2000 r.p.m. for 10 minutes. Concomitantly determine the absorbance of the supernatant liquid and of a standard solution of NF Diphenoxylate Hydrochloride, in the same medium, at a concentration of about 250 mcg. per ml., in 1-cm. cells, at the maximum at about 257 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{30}H_{32}N_2O_2 . HCl$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of diphenoxylate hydrochloride per tablet; D is the exact concentration, in mcg. per ml., of diphenoxylate hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the standard solution.

Assay for diphenoxylate hydrochloride—Weigh and finely powder not less than 60 Diphenoxylate Hydrochloride and Atropine Sulfate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 150 mg. of diphenoxylate hydrochloride, to a 250-ml. separator, add 100 ml. of water and 1 ml. of diluted hydrochloric acid, and extract with five 25-ml. portions of a 9:1 mixture of chloroform and isopropanol, shaking each portion for at least 2 minutes. After each extraction transfer the bottom chloroform layer to a second separator, filtering each portion through a sintered-glass filter. Rinse the filter with a few ml. of chloroform, add the rinsings to the chloroform solution, and extract the combined chloroform solutions with two 25-ml. portions of water. Discard the washings, and evaporate the chloroform in a beaker on a steam bath to a volume of about 5 ml. Add 5 ml. of mercuric acetate T.S. and 100 ml. of glacial acetic acid, and titrate with 0.05 *N* perchloric acid in dioxane, determining the end-point potentiometrically. Each ml. of 0.05 *N* perchloric acid is equivalent to 24.45 mg. of $C_{30}H_{32}N_2O_2 . HCl$.

Assay for atropine sulfate—

p-Dimethylaminobenzaldehyde solution and *Standard stock solution*—Prepare as directed in the *Assay for atropine sulfate* under *Diphenoxylate Hydrochloride and Atropine Sulfate Solution*, page 256.

Diluted standard preparation—Transfer 5.0 ml. of *Standard stock solution* to a 100-ml. volumetric flask, dilute to volume with 0.1 *N* sulfuric acid, mix, and continue as directed under *Assay preparation*, beginning with "To the flask add 2 ml. of chloroform, and mix by inversion and shaking."

Assay preparation—Weigh and finely powder not less than 50 Diphenoxylate Hydrochloride and Atropine Sulfate Tablets. Transfer a portion of the powder, equivalent to about 1.25 mg. of atropine sulfate, to a 100-ml. volumetric flask, add 40 ml. of 0.1 *N* sulfuric acid, shake vigorously for 3 minutes, dilute to volume with 0.1 *N* sulfuric acid, and mix. To the flask add 2 ml. of chloroform, and mix by inversion and shaking. Pour the entire contents of the flask, without rinsing, into a 250-ml. centrifuge cup, cover with a rubber cap, and centrifuge at 1600 r.p.m. for 10 minutes. Carefully decant the aqueous solution into a 250-ml. beaker, retaining the chloroform in the centrifuge cup. Filter the aqueous solution, discarding the first 10 ml. of filtrate. Transfer 40.0 ml. of the subsequent filtrate to a 250-ml. separator, and extract with two 25-ml. portions of a 9:1 mixture of chloroform and isopropanol, combining the extracts in another separator. Do not discard the aqueous phase. Wash the combined extracts with 10 ml. of 0.1 *N* sulfuric acid, add the washing to the original aqueous phase, and then discard the chloroform. Make the combined aqueous solution alkaline with ammonia T.S., and then extract the alkaline solution with five 20-ml. portions of the chloroform-isopropanol 9:1 mixture. Wash the combined extracts with 20 ml. of water, and discard the washing. Extract the chloroform solution with one 40-ml. portion and one 25-ml. portion of 0.1 *N* sulfuric acid, combine the acid extracts in a separate separator, and then discard the chloroform phase. Make the acid extracts alkaline with ammonia T.S., and then extract with five 20-ml. portions of chloroform. Wash the combined chloroform extracts with 20 ml. of water, discard the washing, and then transfer the chloroform layer to a 250-ml. beaker. Evaporate the solution to dryness on a hot plate with the aid of a stream of air, and dissolve the residue in sufficient chloroform to make 10.0 ml.

Procedure—Proceed as directed for *Procedure* in the *Assay for atropine sulfate* under *Diphenoxylate Hydrochloride and Atropine Sulfate Solution,* page 256. Calculate the quantity, in mg., of $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$ in the portion of Tablets taken by the formula $0.025C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Diphenoxylate Hydrochloride and Atropine Sulfate Tablets in well-closed, light-resistant containers.

Tablets available—Diphenoxylate Hydrochloride and Atropine Sulfate Tablets usually available contain the following amount of diphenoxylate hydrochloride: 2.5 mg.; and of atropine sulfate: 25 mcg.

CATEGORY and DOSE—See Diphenoxylate Hydrochloride.

Diphenylhydantoin Oral Suspension

Diphenylhydantoin Oral Suspension is diphenylhydantoin suspended in a suitable medium. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{12}N_2O_2$.

Identification—

A: Shake a volume of Diphenylhydantoin Oral Suspension, equivalent to about 100 mg. of diphenylhydantoin, with 50 ml. of a 1 in 2 mixture of ether and chloroform in a separator, evaporate the extract to dryness, and dry at 105° in vacuum for 4 hours: the diphenylhydantoin so obtained melts between 292° and 299°, with some decomposition, page 814.

B: Dissolve 100 mg. of the residue obtained in *Identification test A* in 100 ml. of chloroform, with slight warming if necessary. To 5 ml. of this solution add 0.2 ml. of a freshly prepared 1 in 100 solution of cobaltous acetate in methanol and 1 ml. of a freshly prepared 1 in 20 solution of isopropylamine in methanol, and mix: a violet to red-violet color is produced.

Assay—Measure accurately a volume of Diphenylhydantoin Oral Suspension, equivalent to between 125 mg. and 200 mg. of diphenylhydantoin, and transfer to a separator. Add 15 ml. of water, mix, and extract with 80-ml. of a 1 in 2 mixture of ether and chloroform, collecting the extract in a 500-ml. separator. Complete the extraction with successive 40-ml. portions of the ether-chloroform mixture until a small portion of the extract does not leave a residue when evaporated in a watch glass. Wash the combined extracts with two 10-ml. portions of sodium bicarbonate solution (1 in 50), discard the wash solution, and then filter the extract through cotton previously moistened with the extraction mixture. Evaporate the filtered extract on a steam bath with the aid of a current of air, dry the residue at 105° in vacuum for 2 hours, and cool. Dissolve in 50 ml. of dimethylformamide, add 3 drops of a saturated solution of azo-violet in benzene, and titrate with 0.1 *N* sodium methoxide to a blue end-point.

Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium methoxide is equivalent to 25.23 mg. of $C_{15}H_{12}N_2O_2$.

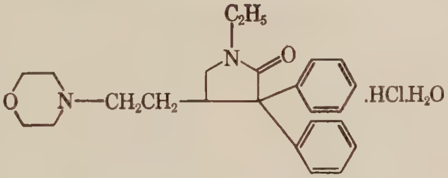
Packaging and storage—Preserve Diphenylhydantoin Oral Suspension in tight containers. Avoid freezing.

Suspensions available—Diphenylhydantoin Oral Suspension usually available contains the following amounts of diphenylhydantoin: 6, 20, and 25 mg. in 1 ml.

CATEGORY—Anticonvulsant.

USUAL DOSE OF DIPHENYLHYDANTOIN—**100 mg.** up to four times a day.

Doxapram Hydrochloride*



1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone Monohydrochloride

$C_{24}H_{30}N_2O_2 . HCl . H_2O$ Mol. wt. 433.00

Doxapram Hydrochloride, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{24}H_{30}N_2O_2 . HCl$.

Description—Doxapram Hydrochloride occurs as a white to off-white, odorless, crystalline powder.

Solubility—Doxapram Hydrochloride is soluble in water and sparingly soluble in alcohol. It is soluble in chloroform and practically insoluble in ether.

Melting range, page 814—Doxapram Hydrochloride melts within a range of 2° between 217° and 221°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Doxapram Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Doxapram Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2500 solution of Doxapram Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Doxapram Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 258 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Doxapram Hydrochloride (1 in 100) is between 3.5 and 5.0.

Loss on drying, page 814—Dry Doxapram Hydrochloride at 105° for 2 hours: it loses not less than 3 percent and not more than 4.5 percent of its weight.

Residue on ignition, page 858—Doxapram Hydrochloride yields not more than 0.3 percent of residue on ignition.

Arsenic—A *Test Preparation* prepared with 2 g. of Doxapram Hydrochloride, as directed for organic compounds, meets the requirements of the *Arsenic Test,* page 777 (5 parts per million As).

Heavy metals, *Method II,* page 806—The heavy metals limit for Doxapram Hydrochloride is 20 parts per million.

Assay—Dissolve about 800 mg. of Doxapram Hydrochloride, previously dried for 2 hours at 105° and accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S. and 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 41.50 mg. of $C_{24}H_{30}N_2O_2 \cdot HCl$.

Packaging and storage—Preserve Doxapram Hydrochloride in tight containers.

CATEGORY—Respiratory stimulant.

USUAL DOSE RANGE—Intravenous, **500 mcg.** to **1 mg. per kg.** of body weight given as a single injection or **1.5** to **2.0 mg. per kg.** of body weight given as injections of **500 mcg.** to **1.0 mg. per kg.** of body weight at 5-minute intervals.

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* Patented. See notice, page ii.

Doxapram Hydrochloride Injection

Doxapram Hydrochloride Injection is a sterile solution of doxapram hydrochloride in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{24}H_{30}N_2O_2 . HCl$.

Identification—The ultraviolet absorption spectrum of the solution prepared from Doxapram Hydrochloride Injection for measurement of absorbance in the *Assay* exhibits ultraviolet absorption maxima and minima at the same wavelengths as that of NF Doxapram Hydrochloride Reference Standard, similarly measured.

pH, page 824—The pH of Doxapram Hydrochloride Injection is between 3.5 and 5.0.

Other requirements—Doxapram Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—Transfer an accurately measured volume of Doxapram Hydrochloride Injection, equivalent to about 100 mg. of doxapram hydrochloride, to a 250-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Doxapram Hydrochloride Reference Standard, in the same medium, at a concentration of about 400 mcg. per ml., in 1-cm. cells, at the maximum at about 258 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{24}H_{30}N_2O_2.HCl$ in each ml. of the Injection taken by the formula $0.25 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Injection taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

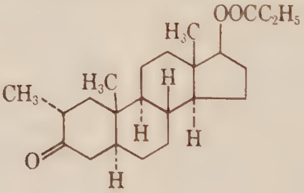
Packaging and storage—Preserve Doxapram Hydrochloride Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injection available—Doxapram Hydrochloride Injection usually available contains the following amount of doxapram hydrochloride: 400 mg. in 20 ml.

CATEGORY and DOSE—See Doxapram Hydrochloride.

Dried Sodium Phosphate, page 655
Dried Yeast, page 764
Dried Yeast Tablets, page 765

Dromostanolone Propionate*



17β-Hydroxy-2α-methyl-5α-androstan-3-one Propionate

$C_{23}H_{36}O_3$ Mol. wt. 360.54

Dromostanolone Propionate contains not less than 95.0 percent and not more than 102.0 percent of $C_{23}H_{36}O_3$, calculated on the dried basis.

Description—Dromostanolone Propionate occurs as a white to creamy white, crystalline powder. It is odorless or has a faint odor.

Solubility—Dromostanolone Propionate is practically insoluble in water. It is soluble in chloroform, in ether, and in methanol.

Identification—Prepare a solution of Dromostanolone Propionate in chloroform containing 10 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot

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* Patented. See notice, page ii.

10 µl. of this solution and 10 µl. of a chloroform solution of NF Dromostanolone Propionate Reference Standard containing 10 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and ethyl acetate (9:1) until the solvent front has moved to within about 2.5 cm. from the top of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots by lightly spraying with a 1 in 100 solution of vanillin in 50 percent phosphoric acid, and heating at 105° for 15 minutes. Observe the plate under longwave ultraviolet light: the R_f value of the main spot obtained from the sample corresponds to that obtained from the Reference Standard solution.

Melting range, page 814—Dromostanolone Propionate melts within a range of 4° between 127° and 133°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Dromostanolone Propionate, previously dried in vacuum at 40° for 16 hours, exhibits maxima only at the same wavelengths as that of NF Dromostanolone Propionate Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Dromostanolone Propionate, previously dried in vacuum at 40° for 16 hours, determined in a solution in chloroform containing 200 mg. of dromostanolone propionate in each 10 ml., is between +22° and +28°.

Loss on drying, page 814—Dry Dromostanolone Propionate in vacuum at 40° for 16 hours: it loses not more than 1 percent of its weight.

Assay—Transfer about 25 mg. of Dromostanolone Propionate, accurately weighed, to a 10-ml. volumetric flask, add chloroform to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Dromostanolone Propionate Reference Standard, in the same medium, at a concentration of about 2.5 mg. per ml., in 1-mm. cells, at the maximum at about 5.9 µ, with a suitable infrared spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{23}H_{36}O_3$ in the Dromostanolone Propionate taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Dromostanolone Propionate in tight containers, protected from light.

CATEGORY—Antineoplastic.

USUAL DOSE—Intramuscular, **100 mg.** three times a week.

Dromostanolone Propionate Injection

Dromostanolone Propionate Injection is a sterile solution of dromostanolone propionate in a suitable oil. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{23}H_{36}O_3$. It contains phenol as a preservative.

Identification—The infrared absorption spectrum of the *Assay preparation*, prepared as directed in the *Assay*, exhibits maxima and minima at the same wavelengths as that of the *Standard preparation*, prepared as directed in the *Assay*.

Other requirements—Dromostanolone Propionate Injection meets the requirements under *Injections*, page 810.

Assay—

Adsorbent—Pack a pledget of glass wool in the stem of a suitable funnel, fill the funnel to within 2.5 cm. of the top with 60 to 100-mesh chromatographic magnesium silicate, and wash thoroughly with hot hydrochloric acid until the last washing is colorless. Wash with water until free from chloride, then wash with methanol, and finally with a mixture of equal volumes of benzene and carbon tetrachloride. Spread in a thin layer, and dry at 100° for 6 hours.

Chromatographic column—Pack a pledget of glass wool in the base of a 1.2 × 30-cm. chromatographic tube equipped with a stopcock. To the tube add a slurry prepared by mixing 4 g. of *Adsorbent* with a mixture of equal volumes of benzene and carbon tetrachloride, taking precautions to avoid the formation of air pockets or channels. Wash down the sides of the tube with the benzene-carbon tetrachloride mixture, allow the adsorbent to settle, and tap the tube gently and uniformly. Insert a pledget of glass wool in the top of the tube. (*Caution:* Do not allow the top of the adsorbent to become dry during the preparation of the column.)

Standard preparation—Dissolve about 12.5 mg. of NF Dromostanolone Propionate Reference Standard, accurately weighed, in 80 percent methanol in a 25-ml. volumetric flask. Dilute to volume with 80 percent methanol, and mix. Continue as directed under *Assay preparation*, beginning with "Transfer 10.0 ml. of this solution to a 25-ml. conical flask. . . ."

Assay preparation—Transfer an accurately measured volume of Dromostanolone Propionate Injection, equivalent to about 50 mg. of dromostanolone propionate, to a 50-ml. centrifuge tube, add 20 ml. of 80 percent methanol, and shake for 5 minutes. Centrifuge for 3 minutes at 1500 r.p.m., then carefully decant into a 100-ml. volumetric flask. Extract the oil phase with three additional 20-ml. portions of 80 percent methanol, decanting into the volumetric flask. Dilute the solution in the flask to volume with 80 percent methanol, and mix. Transfer 10.0 ml. of this solution to a 25-ml. conical flask, and evaporate to dryness using mild heat and a stream of air. Toward the end of the evaporation add several small portions of dehydrated methanol to facilitate evaporation of the residual water. Dissolve the residue in about 6 ml. of a mixture of equal volumes of benzene and carbon tetrachloride, and add this solution to the top of the chromatographic column, washing the flask with two 2-ml. portions of the same mixture and adding the washings to the column. Just as the solution disappears into the plug, add to the column 40 ml. of the benzene-carbon tetrachloride mixture to wash the column, and discard the eluate. Elute the dromostanolone propionate by adding to the column a mixture of alcohol and chloroform (1:20), and collect 25.0 ml. of eluate. Evaporate to dryness using mild heat and a stream of air, and dissolve the residue in 2.0 ml. of chloroform.

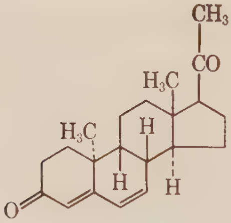
Procedure—Concomitantly determine the absorbances of the solutions in 1-mm. cells, at the maximum at about 5.9 μ, with a suitable infrared spectrophotometer, using chloroform as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{23}H_{36}O_3$ in each ml. of the Injection taken by the formula $20 \times C/V \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Dromostanolone Propionate Injection in single-dose or in multiple-dose containers of Type II or Type III glass, protected from light.

Injections available—Dromostanolone Propionate Injection usually available contains the following amounts of dromostanolone propionate: 50 mg. in 1 ml.; 500 mg. in 10 ml.

CATEGORY and DOSE—See Dromostanolone Propionate.

Dydrogesterone*



9β,10α-Pregna-4,6-diene-3,20-dione

$C_{21}H_{28}O_2$ Mol. wt. 312.46

Dydrogesterone contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{28}O_2$, calculated on the dried basis.

Description—Dydrogesterone occurs as a white to pale yellow, crystalline powder.

Solubility—Dydrogesterone is practically insoluble in water and sparingly soluble in alcohol.

Identification—Dissolve about 50 mg. of Dydrogesterone in 5 ml. of dehydrated alcohol, add about 50 mg. each of hydroxylamine hydrochloride and anhydrous sodium acetate, and reflux gently for 2 hours. Concentrate the liquid to about 3 ml., then add 10 ml. of water, mix, and centrifuge. Wash the precipitate with two 3-ml. portions of warm methanol, and dry at 105° for 1 hour: the dydrogesterone dioxime so obtained melts between 275° and 282° with decomposition (*Class Ia*, page 815).

Melting range, *Class Ia*, page 815—Dydrogesterone melts between 167° and 171°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Dydrogesterone, previously dried in vacuum at 50° for 1 hour, exhibits maxima only at the same wavelengths as that of NF Dydrogesterone Reference Standard, similarly measured.

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* Patented, see notice, p. ii.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 167,000 solution of Dydrogesterone in methanol exhibits maxima and minima at the same wavelengths as that of NF Dydrogesterone Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 285 mμ, do not differ by more than 2.5 percent.

Specific rotation, page 822—The specific rotation of Dydrogesterone, calculated on the dried basis, determined in a solution in chloroform containing 50 mg. in each 10 ml., is between −470° and −500°.

Loss on drying, page 814—Dry Dydrogesterone in vacuum at 50° for 1 hour: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Dydrogesterone yields not more than 0.1 percent of residue on ignition. Retain the residue for the *Heavy metals test.*

Heavy metals, page 806—Dissolve the residue obtained in the test for *Residue on ignition* in 4 drops of diluted hydrochloric acid, add about 5 ml. of water, filter, and wash the residue with sufficient water to make 25 ml.: the heavy metals limit for Dydrogesterone is 20 parts per million.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Dydrogesterone Reference Standard, previously dried in vacuum at 50° for 1 hour.

Test preparation—Weigh accurately about 80 mg. of Dydrogesterone, previously dried in vacuum at 50° for 1 hour, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, spotting 20 μl. each of the *Standard preparation* and of the *Test preparation* and using a solvent system consisting of benzene-acetone (4:1). Determine the absorbance at the maximum at about 285 mμ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Dydrogesterone taken: not more than 3 percent is found.

Assay—

Standard preparation—Dissolve in chloroform a suitable quantity of NF Dydrogesterone Reference Standard, accurately weighed, and dilute quantitatively and stepwise with chloroform to obtain a solution having a concentration of about 20 mcg. per ml. Transfer 5.0 ml. of this solution to a glass-stoppered 50-ml. conical flask.

Assay preparation—Weigh accurately about 100 mg. of Dydrogesterone, dissolve in sufficient chloroform to make 200.0 ml., and mix. Transfer 10.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 5.0 ml. of this last solution to a glass-stoppered 50-ml. conical flask.

Procedure—To each of the flasks containing the *Standard preparation* and the *Assay preparation,* and to a similar flask containing 5.0 ml. of chloroform to serve as the blank, add 10.0 ml. of a solution of 375 mg. of isoniazid and 0.47 ml. of hydrochloric acid in 500 ml. of methanol. Mix, allow to stand for 45 minutes, and concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 420 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{28}O_2$ in the Dydrogesterone taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Dydrogesterone in well-closed containers.

CATEGORY—Progestin.

USUAL DOSE—**10** to **20 mg.** daily in divided doses.

USUAL DOSE RANGE—**10** to **30 mg.**

Dydrogesterone Tablets

Dydrogesterone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{28}O_2$.

Identification—Triturate a quantity of finely powdered Dydrogesterone Tablets, equivalent to about 5 mg. of dydrogesterone, with 10 ml. of chloroform, and filter. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution and 10 μl. of a chloroform solution of NF Dydrogesterone Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of benzene and ether (3:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by viewing under shortwave ultraviolet light: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Disintegration, page 878—The disintegration time limit for Dydrogesterone Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Dydrogesterone Tablets meet the requirements of the content uniformity test for tablets using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask, add 50 ml. of methanol, and heat in a water bath at 60° for 10 minutes with frequent agitation. Remove from the bath, shake mechanically for 20 minutes, and cool. Dilute to volume with methanol, mix, and centrifuge. Dilute a portion of the clear, supernatant liquid with methanol to provide a solution containing approximately 5 mcg. of dydrogesterone per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Dydrogesterone Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells at the maximum at about 285 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{21}H_{28}O_2$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of dydrogesterone in the tablet; D is the exact concentration, in mcg. per ml., of dydrogesterone in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Dydrogesterone,* page 262.

Assay preparation—Weigh and finely powder not less than 10 Dydrogesterone Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of dydrogesterone, to a separator with the aid of about 15 ml. of water, and extract with four 25-ml. portions of chloroform, filtering each extract through chloroform-moistened cotton into a 250-ml. volumetric flask. Dilute the contents of the flask to volume with chloroform, and mix. Transfer 25.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 5.0 ml. of this last solution to a glass-stoppered 50-ml. conical flask.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Dydrogesterone,* page 262. Calculate the quantity, in mg., of $C_{21}H_{28}O_2$ in the portion of Tablets taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

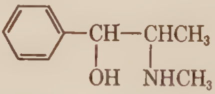
Packaging and storage—Preserve Dydrogesterone Tablets in well-closed containers.

Tablets available—Dydrogesterone Tablets usually available contain the following amounts of dydrogesterone: 5, 10, and 20 mg.

CATEGORY and DOSE—See Dydrogesterone.

Effervescent Sodium Phosphate, page 656

Ephedrine



(−)-*erythro*-α-[1-(Methylamino)ethyl]benzyl Alcohol

$C_{10}H_{15}NO$ Mol. wt. 165.24

Ephedrine is anhydrous or contains not more than one-half molecule of water of hydration. Anhydrous Ephedrine contains not less than 98.5 percent and not more than 100.5 percent of $C_{10}H_{15}NO$. Hydrated Ephedrine contains not less than 98.5 percent and not more than 100.5 percent of $C_{10}H_{15}NO$, calculated on the anhydrous basis.

Description—Ephedrine occurs as an unctuous, almost colorless solid, or white crystals or granules. It gradually decomposes on exposure to light. It melts between 33° and 40°, the variability in the melting point being due to differences in the moisture content, anhydrous Ephedrine having a lower melting point than the hemihydrate of Ephedrine. Its solutions are alkaline to litmus.

Solubility—Ephedrine is soluble in water, in alcohol, in chloroform, and in ether, and is moderately and slowly soluble in liquid petrolatum, the solution in the latter becoming turbid if the Ephedrine contains more than about 1 percent of water.

Identification—

A: Dissolve 10 mg. of Ephedrine in 1 ml. of water with the aid of 1 or 2 drops of diluted hydrochloric acid, and add 0.1 ml. of cupric sulfate T.S. followed by 1 ml. of sodium hydroxide solution (1 in 5): a reddish purple color develops. To the mixture add 1 ml. of ether and shake well: the ether layer is purple and the water layer is blue.

B: Dissolve 50 mg. of Ephedrine in 10 ml. of chloroform, allow the solution to stand overnight in a closely covered vessel, and then let the chloroform evaporate spontaneously: white crystals of ephedrine hydrochloride appear, which, when dissolved in water, respond to the test for *Chloride*, page 808.

Specific rotation, page 822—Dissolve about 500 mg. of Ephedrine in 10 ml. of ether in a tared beaker, add 0.5 ml. of hydrochloric acid, evaporate to dryness, and dry the residue at 105° for 3 hours. The specific rotation of the ephedrine hydrochloride so obtained, calculated on the anhydrous basis, determined in a solution containing 500 mg. in each 10 ml., is between −33° and −35.5°.

Water, page 900—Determine the water content of Hydrated Ephedrine by the titrimetric method (*residual titration procedure*): not less than 4.5 percent and not more than 5.5 percent is found.

Residue on ignition, page 858—Ephedrine yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—A solution of 500 mg. of Ephedrine shows no more chloride than corresponds to 0.2 ml. of 0.02 *N* hydrochloric acid (0.028 percent).

Sulfate—Dissolve 100 mg. of Ephedrine in 40 ml. of water, and add 1 ml. of diluted hydrochloric acid and 1 ml. of barium chloride T.S.: no turbidity develops within 10 minutes.

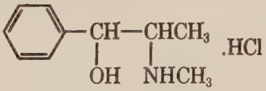
Assay—Dissolve about 500 mg. of Ephedrine, accurately weighed, in 10 ml. of neutralized alcohol, add 5 drops of methyl red T.S., and 40.0 ml. of 0.1 *N* hydrochloric acid. Titrate the excess acid with 0.1 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* hydrochloric acid is equivalent to 16.52 mg. of $C_{10}H_{15}NO$.

Labeling—The label shall declare whether the Ephedrine is hydrated or anhydrous. When the quantity of Ephedrine is indicated in the labeling of any preparation of Ephedrine, this shall be understood to be in terms of anhydrous Ephedrine.

Packaging and storage—Preserve Ephedrine in tight, light-resistant containers, in a cold place.

CATEGORY—Adrenergic (bronchodilator).

Ephedrine Hydrochloride



(−)-*erythro*-α-[1-(Methylamino)ethyl]benzyl Alcohol Hydrochloride

$C_{10}H_{15}NO.HCl$ Mol. wt. 201.70

Ephedrine Hydrochloride, dried at 105° for 3 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{10}H_{15}NO.HCl$.

Description—Ephedrine Hydrochloride occurs as fine, white, odorless crystals or as a powder. It is affected by light.

Solubility—Ephedrine Hydrochloride is freely soluble in water and is soluble in alcohol. It is insoluble in ether.

Identification—

A: Dissolve 10 mg. of Ephedrine Hydrochloride in 1 ml. of water, and add 0.1 ml. of cupric sulfate T.S., followed by 1 ml. of sodium hydroxide solution (1 in 5): a reddish purple color develops. To the mixture add 1 ml. of ether and shake well: the ether layer becomes purple and the water layer blue.

B: A solution of Ephedrine Hydrochloride responds to the tests for *Chloride*, page 808.

Acidity or alkalinity—Dissolve 1 g. of Ephedrine Hydrochloride in 20 ml. of water and add 1 drop of methyl red T.S. If the solution is yellow, it is changed to red by not more than 0.1 ml. of 0.02 *N* sulfuric acid. If the solution is pink, it is changed to yellow by not more than 0.2 ml. of 0.02 *N* sodium hydroxide.

Melting range, page 814—Ephedrine Hydrochloride melts between 217° and 220°.

Specific rotation, page 822—The specific rotation of Ephedrine Hydrochloride, previously dried at 105° for 3 hours, determined in a solution containing 500 mg. of Ephedrine Hydrochloride in each 10 ml., is between $-33°$ and $-35.5°$.

Loss on drying, page 814—Dry Ephedrine Hydrochloride at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Ephedrine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Sulfate—Dissolve 50 mg. of Ephedrine Hydrochloride in 40 ml. of water, and add 1 ml. of diluted hydrochloric acid and 1 ml. of barium chloride T.S.: no turbidity develops within 10 minutes.

Assay—Transfer about 300 mg. of Ephedrine Hydrochloride, previously dried at 105° for 3 hours and accurately weighed, into a separator, and dissolve in 10 ml. of water. Saturate the solution with sodium chloride (about 3 g.), add 5 ml. of sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water saturated with sodium chloride, and filter through chloroform-moistened cotton into a suitable flask. Extract the water wash with 10 ml. of chloroform, and add this extract to the main chloroform extract. Add 3 drops of methanolic methyl red T.S., and titrate with 0.1 *N* perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 20.17 mg. of $C_{10}H_{15}NO.HCl$.

Packaging and storage—Preserve Ephedrine Hydrochloride in well-closed, light-resistant containers.

CATEGORY—Adrenergic (bronchodilator).

USUAL DOSE—**25** to **50 mg.** every 3 or 4 hours.

Ephedrine Hydrochloride, Theophylline, and Phenobarbital Tablets, page 695

Ephedrine Sulfate and Phenobarbital Capsules

Ephedrine Sulfate and Phenobarbital Capsules contain not less than 91.0 percent and not more than 109.0 percent of the labeled amounts of $(C_{10}H_{15}NO)_2.H_2SO_4$ (ephedrine sulfate) and of $C_{12}H_{12}N_2O_3$ (phenobarbital).

Identification—

A: Mix the contents of a sufficient number of Ephedrine Sulfate and Phenobarbital Capsules, equivalent to about 200 mg. of ephedrine sulfate, with 25 ml. of water. Filter into a separator, add 2 ml. of ammonia T.S., and extract with 2 successive 15-ml. portions of chloroform. Filter the chloroform solutions through a chloroform-washed pledget of cotton into a beaker and let the chloroform evaporate spontaneously: white crystals of ephedrine hydrochloride are produced. Dissolve 10 mg. of the crystals in 1 ml. of water, and add 0.1 ml. of cupric sulfate T.S., followed by 1 ml. of sodium hydroxide solution (1 in 5): a reddish purple color develops. To the mixture add 1 ml. of ether and shake well: the ether layer becomes purple and the water layer blue.

B: A solution of the crystals obtained in *Identification test A* responds to the tests for *Chloride*, page 808.

C: Mix the contents of a sufficient number of Ephedrine Sulfate and Phenobarbital Capsules, equivalent to about 500 mg. of phenobarbital, with 25 ml. of water and 4 ml. of sodium hydroxide T.S. Filter into a separator, acidify with hydrochloric acid, and add 1 ml. in excess. Extract with 3 successive 15-ml. portions of chloroform and pass the chloroform solution through a chloroform-moistened filter, collect it in a beaker and evaporate to dryness. The infrared absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of USP Phenobarbital Reference Standard, similarly measured.

Content uniformity, *Method II*, page 798—Ephedrine Sulfate and Phenobarbital Capsules meet the requirements of the content uniformity test for capsules when tested for phenobarbital content, using the following special procedure: Quantitatively transfer the contents of a capsule to a separator, add 15 ml. of water and 5 ml. of diluted hydrochloric acid, and extract with four 25-ml. portions of chloroform, filtering each portion through chloroform-moistened cotton into a 250-ml. volumetric flask. Add chloroform to volume, and mix. Transfer an accurately measured volume of this solution, equivalent to about 1 mg. of phenobarbital, to a beaker, and evaporate just to dryness on a steam bath. Transfer the residue to a 100-ml. volumetric flask with the aid of 5 ml. of alcohol and then with pH 9.6 alkaline borate buffer solution (see page 783), then dilute to volume with the buffer solution, and mix. Concomitantly determine the absorbance of this solution and of a solution of USP Phenobarbital Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 240 mμ, with a suitable spectrophotometer, using pH 9.6 alkaline borate buffer solution as the blank. Calculate the quantity, in mg., of $C_{12}H_{12}N_2O_3$ in the capsule by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of phenobarbital in the capsule; D is the exact concentration, in mcg. per ml., of phenobarbital in the sample solution, based upon the labeled quantity per capsule and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay for phenobarbital—Transfer as completely as possible the contents of not less than 20 Ephedrine Sulfate and Phenobarbital Capsules to a tared weighing bottle, and weigh. Transfer an accurately weighed portion of the powder, equivalent to about 300 mg. of phenobarbital to a separator, and add 10 ml. of water and 1 ml. of 1 N hydrochloric acid, and extract the phenobarbital with four 25-ml. portions of chloroform. Wash the combined chloroform extracts with 5 ml. of water containing 1 drop of diluted hydrochloric acid, and add the washings to the water layer. Retain the water layer for the *Assay for ephedrine sulfate.* Transfer the chloroform extracts to a 125-ml. conical flask and evaporate just to dryness on a steam bath. Add 30 ml. of dimethylformamide, and 4 drops of thymol blue T.S., and titrate with 0.1 N sodium methoxide, using a magnetic stirrer and taking precautions against the absorption of atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N sodium methoxide is equivalent to 23.22 mg. of $C_{12}H_{12}N_2O_3$.

Assay for ephedrine sulfate—Saturate the water layer from the *Assay for phenobarbital* with sodium chloride (about 3 g.), add 5 ml. of sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water saturated with sodium chloride, and filter the chloroform through chloroform-moistened cotton into a suitable flask. Extract the water wash with 10 ml. of chloroform, and add this extract to the main chloroform extract. Add 3 drops of methanolic methyl red T.S., and titrate with 0.1 N perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N perchloric acid is equivalent to 21.43 mg. of $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$.

Packaging and storage—Preserve Ephedrine Sulfate and Phenobarbital Capsules in well-closed containers.

Capsules available—Ephedrine Sulfate and Phenobarbital Capsules usually available contain the following amounts of ephedrine sulfate: 25 and 50 mg.; and of phenobarbital: 15 and 30 mg.

CATEGORY—Adrenergic (bronchodilator).

USUAL INDIVIDUAL DOSE OF EPHEDRINE SULFATE—**25 mg.**; OF PHENOBARBITAL—**30 mg.**

Ephedrine Sulfate Tablets

Ephedrine Sulfate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $(C_{10}H_{15}NO)_2 . H_2SO_4$.

Identification—

A: Triturate a quantity of finely powdered Ephedrine Sulfate Tablets, equivalent to about 200 mg. of ephedrine sulfate, with 15 ml. of warm alcohol, filter, and evaporate the filtrate to dryness on a steam bath. Dissolve 10 mg. of the residue in 1 ml. of water, and add 0.1 ml. of cupric sulfate T.S., followed by 1 ml. of sodium hydroxide solution (1 in 5): a reddish purple color develops. To the mixture add 1 ml. of ether, and shake well: the ether layer becomes purple and the water layer blue.

B: A solution of a portion of the residue obtained in *Identification test A* responds to the tests for *Sulfate,* page 807.

Disintegration, page 878—The disintegration time limit for Ephedrine Sulfate Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Ephedrine Sulfate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 50-ml. volumetric flask, add methanol to volume, and mix by shaking thoroughly. Allow to stand until the undissolved particles settle, then filter, and discard the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol to provide a solution containing approximately 500 mcg. of ephedrine sulfate per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Ephedrine Sulfate Reference Standard, in the same medium, at a concentration of about 500 mcg. per ml., in 1-cm. cells, at the maximum at about 257 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $(C_{10}H_{15}NO)_2.H_2SO_4$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of ephedrine sulfate, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of ephedrine sulfate in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 50 Ephedrine Sulfate Tablets. Weigh accurately a portion of the powder, equivalent to about 1.25 g. of ephedrine sulfate, and transfer to a glass-stoppered 125-ml. conical flask. Add 50.0 ml. of 0.1 N sulfuric acid, shake the mixture, and filter, rejecting the first 20 ml. of filtrate. Transfer 10.0 ml. of the subsequent filtrate to a separator. Saturate the solution with sodium chloride (about 3 g.), add 5 ml. of sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water saturated with sodium chloride, and filter through chloroform-saturated cotton. Extract the water wash with 10 ml. of chloroform, and add to the main chloroform extract. Add 3 drops of methanolic methyl red T.S. to the combined chloroform extracts, and titrate with 0.1 N perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N perchloric acid is equivalent to 21.43 mg. of $(C_{10}H_{15}NO)_2.H_2SO_4$.

Packaging and storage—Preserve Ephedrine Sulfate Tablets in well-closed containers.

Tablets available—Ephedrine Sulfate Tablets usually available contain the following amounts of ephedrine sulfate: 25 and 50 mg.

CATEGORY—Adrenergic (bronchodilator).

USUAL DOSE OF EPHEDRINE SULFATE—**25 mg.**

Ergotamine Tartrate and Caffeine Suppositories

Ergotamine Tartrate and Caffeine Suppositories contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $(C_{33}H_{35}N_5O_5)_2.C_4H_6O_6$ (ergotamine tartrate) and of $C_8H_{10}N_4O_2$ (caffeine).

Identification—Melt an Ergotamine Tartrate and Caffeine Suppository in 10 ml. of hot tartaric acid solution (1 in 100), and mix well. Chill the mixture until the layer of oil has hardened, then filter, and divide the filtrate into two parts.

A: To one part of the filtrate add 10 ml. of *p*-dimethylaminobenzaldehyde T.S.: a blue color develops (*presence of ergotamine tartrate*).

B: Transfer the remaining part of the filtrate to a small evaporating dish, evaporate to dryness on a steam bath, add 1 ml. of hydrochloric acid and 100 mg. of potassium chlorate, and re-evaporate. Invert the dish over a vessel containing stronger ammonia water: the residue acquires a purple color, which disappears upon the addition of a solution of fixed alkali (*presence of caffeine*).

Assay—[NOTE: Conduct the analysis for ergotamine tartrate with a minimum exposure to light.]

Preparation of chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (22 × 250-mm. test tube to which is fused a 5-cm. length of 6 or 8-mm. tubing) with the aid of a tamping rod of stainless steel, aluminum, or glass, at least 30 cm. long and having a disk with a diameter about 1 mm. less than that of the chromatographic tube. Prepare a layer of adsorbent by intimately mixing 4 g. of purified siliceous earth with 3.0 ml. of 50 percent (w/w) citric acid solution, and then transfer the mixture to the chromatographic tube in two portions, packing each portion lightly with the tamping rod. Prepare a second layer of adsorbent in a similar manner, using 2 g. of purified siliceous earth and 2.0 ml. of potassium alum solution (prepared by dissolving 12 g. of potassium alum in sufficient water to make 1000 ml., and adjusting to pH 3.5 ± 0.2 if necessary). Transfer this mixture to the chromatographic tube, placing it on top of the first layer, and pack uniformly with the tamping rod. Finally, intimately mix 2 g. of purified siliceous earth with 2.0 ml. of water, transfer to the chromatographic tube on top of the second layer, and pack uniformly with the tamping rod.

Alcoholic tartrate solution—Just prior to use, mix equal volumes of tartaric acid solution (1 in 100) and alcohol.

Ergonovine maleate standard preparation—Transfer to a 500-ml. volumetric flask about 16.8 mg. of USP Ergonovine Maleate Reference Standard, previously dried over silica gel for 4 hours and accurately weighed, add *Alcoholic tartrate solution* to volume, and mix.

Caffeine standard preparation—Transfer to a 250-ml. volumetric flask about 40 mg. of NF Caffeine Reference Standard, previously dried at 80° for 4 hours and accurately weighed, add chloroform to volume, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparations—Transfer a number of Ergotamine Tartrate and Caffeine Suppositories, equivalent to about 10 mg. of ergotamine tartrate, to a 250-ml. separator, add 100 ml. of ether, and shake gently until the suppositories are completely dispersed. Extract with one 50-ml. portion and then with five 10-ml. portions of tartaric acid solution (1 in 100), collecting the extracts in a second 250-ml. separator. Wash the combined extracts with 10 ml. of ether, and transfer the tartaric acid layer to a 200-ml. volumetric flask. Wash the ether layer with 10 ml. of tartaric acid solution (1 in 100), add the washing to the 200-ml. volumetric flask, dilute to volume with tartaric acid solution (1 in 100), and mix. Discard the ether layer. Transfer 40.0 ml. of the tartaric acid solution to a 125-ml. separator, and add at least 25 ml. of sodium bicarbonate solution (1 in 10) to make the sample solution alkaline. Extract with four 30-ml. portions of chloroform, passing each extract through the prepared chromatographic column, and collecting the eluates in a 250-ml. volumetric flask. Rinse the column with several small portions of water-washed chloroform, collecting the chloroform in the 250-ml. volumetric flask. Dilute to volume with chloroform, and mix. Transfer 20.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this last solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Label this solution as the *Caffeine assay preparation*.

Extrude the siliceous earth from the column, by means of slight air pressure, into a 400-ml. beaker, and rinse the walls of the column with 25 ml. of water, adding the rinsings to the beaker. To the beaker add, while stirring, 8 g. of sodium bicarbonate in small portions to prevent excess foaming, and then quantitatively transfer the mixture to a 250-ml. separator with the aid of water. Extract with five 15-ml. portions of chloroform, filtering each extract into a 200-ml. volumetric flask. Dilute to volume with chloroform, and mix. Evaporate a 25.0-ml. portion of this solution to dryness in a 50-ml. conical flask with the aid of a current of air, without heating. Dissolve the residue in 5.0 ml. of *Alcoholic tartrate solution*, and label the resulting solution as the *Ergotamine tartrate assay preparation*. Use this solution without delay in the *Procedure for ergotamine tartrate*.

Procedure for caffeine—Concomitantly determine the absorbance of the *Caffeine standard preparation* and of the *Caffeine assay preparation* in 1-cm. cells, at the maximum at about 276 mμ, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the *Caffeine standard preparation* as A_S and that of the *Caffeine assay preparation* as A_U. Calculate the quantity, in mg., of $C_8H_{10}N_4O_2$ in the Suppositories taken by the formula $62.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Caffeine standard preparation*.

Procedure for ergotamine tartrate—Transfer 5.0 ml. each of the *Ergonovine maleate standard preparation* and of *Alcoholic tartrate solution*, to serve as the blank, to separate 50-ml. conical flasks. Place these flasks and the flask containing the *Ergotamine tartrate assay preparation* in an ice bath, and add, dropwise with continuous swirling, 10.0 ml. of *p*-dimethylaminobenzaldehyde T.S. Stopper the flasks, shake to mix, and allow to stand in the dark for at least 30 minutes but no longer than 60 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 545 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Ergonovine maleate standard preparation* as A_S and that from the *Ergotamine tartrate assay preparation* as A_U. Calculate the quantity, in mg., of $(C_{33}H_{35}N_5O_5)_2 . C_4H_6O_6$ in the Suppositories taken by the formula $0.2C \times 1.488 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Ergonovine maleate standard preparation*, and 1.488 is the ratio of one-half the molecular weight of ergotamine tartrate to the molecular weight of ergonovine maleate.

Packaging and storage—Preserve Ergotamine Tartrate and Caffeine Suppositories in tight containers at temperatures below 25°. Do not expose unwrapped Suppositories to sunlight.

Suppositories available—Ergotamine Tartrate and Caffeine Suppositories usually available contain 2 mg. of ergotamine tartrate and 100 mg. of caffeine.

Category—Antiadrenergic-central stimulant (specific analgesic for migraine).

Usual dose—Rectal, **2 mg.** of ergotamine tartrate with **100 mg.** of caffeine, this dose may be repeated once only in 1 hour if necessary.

Ergotamine Tartrate and Caffeine Tablets

Ergotamine Tartrate and Caffeine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $(C_{33}H_{35}N_5O_5)_2.C_4H_6O_6$ (ergotamine tartrate) and of $C_8H_{10}N_4O_2$ (caffeine).

Identification—Crush an Ergotamine Tartrate and Caffeine Tablet, shake it with 10 ml. of chloroform and 3 drops of stronger ammonia water, and filter. Divide the filtrate into two parts in small evaporating dishes, and evaporate to dryness on a steam bath.

A: Mix one of the residues with 5 ml. of tartaric acid solution (1 in 100), and add 10 ml. of *p*-dimethylaminobenzaldehyde T.S.: a blue color develops (*presence of ergotamine tartrate*).

B: To the other residue add 1 ml. of hydrochloric acid and 100 mg. of potassium chlorate, and evaporate to dryness on a steam bath. Invert the dish over a vessel containing stronger ammonia water: the residue acquires a purple color, which disappears upon the addition of a solution of fixed alkali (*presence of caffeine*).

Disintegration, page 878—The disintegration time limit for Ergotamine Tartrate and Caffeine Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Ergotamine Tartrate and Caffeine Tablets meet the requirements of the content uniformity test for tablets with respect to ergotamine tartrate content.

Assay—[Note: Conduct the analysis of ergotamine tartrate with a minimum exposure to light.]

Preparation of chromatographic columns—

Column A—Pack a pledget of fine glass wool in the base of a chromatographic tube (22 × 250-mm. test tube to which is fused a 5-cm. length of 6 or 8-mm. tubing) with the aid of a tamping rod of stainless steel, aluminum, or glass, at least 30 cm. long and having a disk with a diameter about 1 mm. less than that of the chromatographic tube.

Weigh and finely powder not less than 10 Ergotamine Tartrate and Caffeine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 1 mg. of ergotamine tartrate, to a 100-ml. beaker, add 5.0 ml. of tartaric acid solution (1 in 100), and allow to stand for 30 minutes. Add 5 ml. of chloroform and 1.5 ml. or more of sodium bicarbonate solution (1 in 10) to make the aqueous phase alkaline, and mix. Add 7 g. of purified siliceous earth, and mix intimately. Transfer the mixture to the chromatographic tube in three portions, packing each portion lightly with the tamping rod. Wash the tamping rod and the sides of the beaker with 5 ml. of chloroform, mix the chloroform in the beaker with 3 g. of purified siliceous earth, transfer to the chromatographic tube, and pack uniformly.

Column B—Pack a pledget of fine glass wool in the base of a second chromatographic tube of the size described under *Column A*. Prepare a layer of adsorbent by mixing intimately 4 g. of purified siliceous earth with 3.0 ml. of 50 percent (w/w) citric acid solution, and then transfer to the second chromatographic tube in two portions, packing each portion lightly with a tamping rod. Prepare a second adsorbent layer in a similar manner, using 2 g. of purified siliceous earth and 2.0 ml. of potassium alum solution (prepared by dissolving 12 g. of potassium alum in sufficient water to make 1000 ml., and adjusting the pH to 3.5 ± 0.2 if necessary). Transfer this mixture to the chromatographic tube, placing it on top of the first layer, and pack uniformly with the tamping rod. Finally, intimately mix 2 g. of purified siliceous earth with 2.0 ml. of water, transfer to the chromatographic tube on top of the second layer, and pack uniformly with the tamping rod.

Mount *Column A* directly over *Column B*.

Alcoholic tartrate solution, Ergonovine maleate standard preparation, and *Caffeine standard preparation*—Prepare as directed in the *Assay* under *Ergotamine Tartrate and Caffeine Suppositories*, page 268.

Assay preparations—Add 50 ml. of water-washed ether to *Column A*, allowing the eluate to pass through *Column B* and collecting the final eluate in a 250-ml. volumetric flask. In the same manner, pass 50 ml. of water-washed chloroform through the columns, collecting the final eluate in the 250-ml. volumetric flask containing the ether eluate. Rinse the tip of the stem of *Column A* with a few ml. of water-washed chloroform, adding the rinsings to the 250-ml. volumetric flask. Discard *Column A*. Allow *Column B* to drain completely into the 250-ml.

volumetric flask, and then rinse the walls of the column with a few ml. of water-washed chloroform, followed by 25 ml. of the same solvent to wash the entire column, collecting the eluate in the 250-ml. volumetric flask. Retain *Column B*. Dilute the solution in the volumetric flask to volume with chloroform, and mix. Transfer 20.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this last solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Label this final solution as the *Caffeine assay preparation*.

Extrude the siliceous earth from *Column B*, by means of slight air pressure, into a 400-ml. beaker, and rinse the walls of the column with 25 ml. of water, adding the rinsings to the beaker. To the beaker add, while stirring, 8 g. of sodium bicarbonate in small portions to prevent excess foaming, and then quantitatively transfer the solution to a 250-ml. separator with the aid of water. Extract with five 15-ml. portions of chloroform, filtering each extract into a 100-ml. volumetric flask. Dilute to volume with chloroform, and mix. Evaporate a 25.0-ml. portion of this solution to dryness in a 50-ml. conical flask with the aid of a current of air, without heating. Dissolve the residue in 5.0 ml. of *Alcoholic tartrate solution*, and label the resulting solution as the *Ergotamine tartrate assay preparation*. Use this solution without delay in the *Procedure for ergotamine tartrate*.

Procedure for caffeine—Proceed as directed for *Procedure for caffeine* in the *Assay* under *Ergotamine Tartrate and Caffeine Suppositories*, page 268. Calculate the quantity, in mg., of $C_8H_{10}N_4O_2$ in the portion of Tablets taken by the formula $12.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Caffeine standard preparation*.

Procedure for ergotamine tartrate—Proceed as directed for *Procedure for ergotamine tartrate* in the *Assay* under *Ergotamine Tartrate and Caffeine Suppositories*, page 268. Calculate the quantity, in mg., of $(C_{33}H_{35}N_5O_5)_2 . C_4H_6O_6$ in the portion of Tablets taken by the formula $0.02C \times 1.488 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Ergonovine maleate standard preparation*, and 1.488 is the ratio of one-half the molecular weight of ergotamine tartrate to the molecular weight of ergonovine maleate.

Packaging and storage—Preserve Ergotamine Tartrate and Caffeine Tablets in well-closed, light-resistant containers.

Tablets available—Ergotamine Tartrate and Caffeine Tablets usually available contain 1 mg. of ergotamine tartrate and 100 mg. of caffeine.

CATEGORY—Antiadrenergic-central stimulant (specific analgesic for migraine).

USUAL DOSE—Initial, **2 mg.** of ergotamine tartrate and **200 mg.** of caffeine, followed by one-half this dose every 30 minutes until relief is obtained, but not to exceed a total dose of 6 mg. of ergotamine tartrate.

Eriodictyon

Eriodictyon is the dried leaf of *Eriodictyon californicum* (Hooker et Arnott) Torrey (Fam. *Hydrophyllaceæ*).

Unground Eriodictyon usually occurs in fragments, but when it is entire, the leaf is lanceolate, from 5 to 15 cm. in length and from 1 to 3 cm. in breadth. The apex is acute and the base tapers slightly into a short petiole. The margin is irregularly serrate or crenate-dentate. The upper surface is weak brown to moderate olive-brown, and is covered with a more or less glistening resin while the lower surface is yellowish brown to weak greenish yellow, reticulate with conspicuous veins, and minutely tomentose between the reticulations. The leaf is quite thick and brittle. Eriodictyon has an aromatic odor and a balsamic, bitter taste which becomes sweetish and slightly acrid.

Histology—In Eriodictyon the upper epidermis consists of large cells, the outer walls of which are very uneven, as seen in cross-section, owing to indentations, which in surface view appear as striations. Also located on the upper epidermis are numerous, deep-seated glandular hairs, each possessing a 1- to 3-celled stalk, and a multicellular glandular head consisting usually of 8 cells. Nonglandular hairs are absent on the upper epidermis. The palisade cells are very narrow and are arranged in rows from 2 to 6 cells deep. Interspersed between them are regularly arranged perpendicular rows of parenchyma cells, each cell generally containing a calcium oxalate rosette aggregate. The cells of the spongy parenchyma comprise but a few layers and the vascular tissues are not strongly developed except in the midrib and in the more prominent veins. In cross-section, the lower surface shows numerous sinuses lined by the lower epidermis from which emanate occasional deep-seated glandular hairs and many curved nonglandular hairs, the latter nearly filling the sinuses and frequently concealing the stomata.

Powdered Eriodictyon is yellow. It

contains unicellular, undulate, thick-walled, non-glandular hairs up to 250 μ in length and up to 10 μ in width; glandular hairs with 1- to 3-celled stalks and multicellular heads consisting usually of 8 cells, the heads being up to 120 μ in diameter; fragments of palisade tissue containing regularly arranged columnar parenchyma cells, most of which contain a calcium oxalate rosette aggregate; and vessels with spiral thickenings or simple pits usually associated with lignified fibers. The calcium oxalate rosette aggregates are numerous and are from 5 to 30 μ in diameter.

Eriodictyon californicum stems—The stems show a subepidermal cork; a primary cortex of 10 to 20 rows of rounded parenchyma cells; a pericycle containing a nearly closed ring of lignified sclerenchyma; a narrow phloem; a xylem region consisting of wood-wedges separated by xylem rays 1 cell in width, the wood-wedges containing numerous strongly lignified wood fibers and spiral and pitted vessels; and a broad pith.

Stems—Eriodictyon contains not more than 5 percent of its stems.

Acid-insoluble ash, page 388—Eriodictyon yields not more than 2 percent of acid-insoluble ash.

Foreign organic matter, page 388—Eriodictyon contains not more than 2 percent of foreign organic matter other than stems.

CATEGORY—Flavor.

Eriodictyon Fluidextract

Eriodictyon, in moderately coarse powder	1000 g.

Prepare the Fluidextract by Process A, page 329, using a mixture of 4 volumes of alcohol and 1 volume of water as the menstruum. Macerate the drug during 48 hours, then percolate at a moderate rate, and reserve the first 800 ml. of percolate.

Alcohol content, page 372—Eriodictyon Fluidextract contains from 67 to 82 percent, by volume, of C_2H_5OH.

Packaging and storage—Preserve Eriodictyon Fluidextract in tight, light-resistant containers and avoid exposure to direct sunlight or to excessive heat.

CATEGORY—Flavor.

Aromatic Eriodictyon Syrup

Eriodictyon Fluidextract	32	ml.
Potassium Hydroxide Solution (1 in 20)	25	ml.
Compound Cardamom Tincture	65	ml.
Lemon Oil	0.5	ml.
Clove Oil	1	ml.
Alcohol	32	ml.
Sucrose	800	g.
Magnesium Carbonate	5	g.
Purified Water, a sufficient quantity,		
To make	1000	ml.

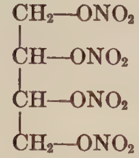
Dissolve the oils in the alcohol, add the fluidextract and the tincture, then the potassium hydroxide solution and 325 ml. of purified water. Add the magnesium carbonate, shake the mixture, allow it to stand overnight, filter, and add sufficient purified water through the filter to make the liquid measure 500 ml. Pour this filtrate upon the sucrose contained in a bottle, and dissolve by placing the bottle in hot water, and agitating the contents frequently. Cool the solution, and add sufficient purified water to make the product measure 1000 ml.

Alcohol content, page 372—Aromatic Eriodictyon Syrup contains from 6 to 8 percent, by volume, of C_2H_5OH.

Packaging and storage—Preserve Aromatic Eriodictyon Syrup in tight, light-resistant containers, and avoid excessive heat.

CATEGORY—Vehicle.

Diluted Erythrityl Tetranitrate



$$\begin{array}{l} CH_2—ONO_2 \\ | \\ CH—ONO_2 \\ | \\ CH—ONO_2 \\ | \\ CH_2—ONO_2 \end{array}$$

Erythritol Tetranitrate

$C_4H_6N_4O_{12}$ Mol. wt. 302.11

Diluted Erythrityl Tetranitrate is a dry mixture of erythrityl tetranitrate ($C_4H_6N_4O_{12}$) with lactose or other suitable inert excipients, to permit safe handling and compliance with federal Interstate Commerce Commission regulations pertaining to interstate shipment. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_4H_6N_4O_{12}$.

Caution: Undiluted erythrityl tetranitrate is a powerful explosive, and proper precautions must be taken in handling. It can be exploded by percussion or by excessive heat. Only extremely small quantities should be isolated.

Description—Diluted Erythrityl Tetranitrate occurs as a white powder having a slight odor of nitric oxides.

Solubility—Undiluted erythrityl tetranitrate is soluble in acetone, in acetonitrile, and in alcohol, and it is slightly soluble in alcohol and is practically insoluble in water.

Identification—Transfer an amount of Diluted Erythrityl Tetranitrate, equivalent to about 10 mg. of erythrityl tetranitrate, to a small separator, add 5 ml. of water and 1 ml. of diluted sulfuric acid, and extract with 25 ml. of chloroform. Transfer the chloroform layer to a small flask containing 1 g. of sodium chloride, shake well, and allow to settle. Transfer 2 ml. of the solution to the surface of 500 mg. of potassium bromide contained in a small beaker, and remove the chloroform by evaporation, using gentle heat: the infrared absorption spectrum of a pressed disk prepared from the residue exhibits maxima at the following wavelengths, in μ: 3.39 (*sh*), 3.45 (*m*), 3.52 (*w*), 6.00 (*s*), 6.12 (*s*), 6.88 (*m*), 7.26 (*m*), 7.45 (*sh*), 7.68 (*s*), 7.81 (*s*), 7.92 (*s*), 8.13 (*sh*), 9.43 (*m*), 9.68 (*s*), 10.16 (*s*), 10.88 (*s*), 11.40 (*s*), 11.99 (*s*), 13.22 (*m*), and 14.25 (*m*).

Assay—

Standard preparation—Transfer about 130 mg. of potassium nitrate, previously dried at 105° for 4 hours and accurately weighed, to a 10-ml. volumetric flask, add water to volume, and mix. Transfer 1.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with glacial acetic acid, and mix.

Assay preparation—Transfer an accurately weighed amount of Diluted Erythrityl Tetranitrate, equivalent to about 10 mg. of erythrityl tetranitrate, to a small separator, add 20 ml. of chloroform and 10 ml. of water, and shake. Drain the chloroform layer into a 50-ml. volumetric flask. Extract the aqueous layer with two 10-ml. portions of chloroform, adding the extracts to the volumetric flask. Dilute the contents of the flask to volume with chloroform, and mix.

Procedure—Transfer 1.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate small beakers. Evaporate the chloroform from the *Assay preparation* with the aid of a current of air and very gentle heat, and then dissolve the residue in 1.0 ml. of glacial acetic acid. To each beaker add 2 ml. of phenoldisulfonic acid T.S., mix, and allow to stand for 15 minutes. Add 8 ml. of water to each beaker, mix, and carefully add 8 ml. of stronger ammonia T.S. Cool, quantitatively transfer the solutions to separate 25-ml. volumetric flasks, dilute each to volume with water, and mix. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 405 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_4H_6N_4O_{12}$ in the Diluted Erythrityl Tetranitrate taken by the formula $0.05C \times 0.7470 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of potassium nitrate in the *Standard preparation*, and 0.7470 is an equivalence factor relating potassium nitrate to erythrityl tetranitrate.

Packaging and storage—Preserve Diluted Erythrityl Tetranitrate in tight containers, and avoid exposure to excessive heat.

Concentrations available—Diluted Erythrityl Tetranitrate usually available contains 11 percent of erythrityl tetranitrate.

Category—Vasodilator.

Usual dose—Oral, initial, **10 mg.** of erythrityl tetranitrate three times a day; sublingual, initial, **5 mg.** of erythrityl tetranitrate three times a day. These doses may be increased in 2 or 3 days if needed.

Erythrityl Tetranitrate Tablets

Erythrityl Tetranitrate Tablets are prepared from diluted erythrityl tetranitrate. They contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_4H_6N_4O_{12}$.

Caution: Undiluted erythrityl tetranitrate is a powerful explosive, and proper precautions must be taken in handling. It can be exploded by percussion or by excessive heat. Only extremely small amounts should be isolated.

Identification—A portion of finely powdered Erythrityl Tetranitrate Tablets, equivalent to about 10 mg. of erythrityl tetranitrate, meets the requirements of the *Identification test* under *Diluted Erythrityl Tetranitrate*, page 273.

Disintegration, page 878—The disintegration time limit for Erythrityl Tetranitrate Tablets, determined without the use of disks, is 10 minutes.

Content uniformity, *Method I*, page 799—Erythrityl Tetranitrate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Diluted Erythrityl Tetranitrate*, page 273.

Assay preparation—Weigh and finely powder not less than 20 Erythrityl Tetranitrate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg. of erythrityl tetranitrate, to a small separator, and continue as directed for *Assay preparation* in the *Assay* under *Diluted Erythrityl Tetranitrate*, page 273, beginning with "... add 20 ml. of chloroform ..."

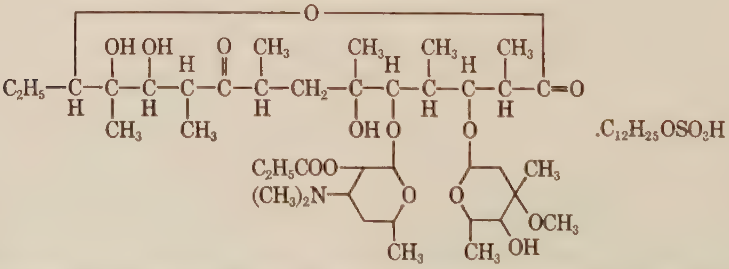
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Diluted Erythrityl Tetranitrate*, page 273. Calculate the quantity, in mg., of $C_4H_6N_4O_{12}$ in the portion of Tablets taken by the formula $0.05C \times 0.7470 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of potassium nitrate in the *Standard preparation*, and 0.7470 is an equivalence factor relating potassium nitrate and erythrityl tetranitrate.

Packaging and storage—Preserve Erythrityl Tetranitrate Tablets in tight containers.

Tablets available—Erythrityl Tetranitrate Tablets usually available contain diluted erythrityl tetranitrate equivalent to the following amounts of erythrityl tetranitrate: 5, 10, and 15 mg.

Category and Dose—See Diluted Erythrityl Tetranitrate.

Erythromycin Estolate*



Erythromycin 2′-Propionate (Ester) Dodecyl Hydrogen Sulfate (1:1) Compound

$C_{40}H_{71}NO_{14} . C_{12}H_{26}O_4S$ Mol. wt. 1056.41

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* Patented. See notice, page ii.

Erythromycin Estolate contains not less than 60.0 percent of $C_{37}H_{67}NO_{13}$ (erythromycin), calculated on the anhydrous basis. Erythromycin Estolate conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Erythromycin Estolate occurs as a white, crystalline powder. It is odorless or practically odorless and is practically tasteless.

Solubility—Erythromycin Estolate is practically insoluble in water. It is soluble in alcohol, in acetone, and in chloroform.

Packaging and storage—Preserve Erythromycin Estolate in tight containers.

CATEGORY—Antibacterial.

USUAL DOSE—The equivalent of **250 mg.** of erythromycin every 6 hours.

USUAL DOSE RANGE—**250** to **500 mg.**

Erythromycin Estolate Capsules

Erythromycin Estolate Capsules contain an amount of erythromycin estolate equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{37}H_{67}NO_{13}$ (erythromycin). Erythromycin Estolate Capsules conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Erythromycin Estolate Capsules in tight containers.

Capsules available—Erythromycin Estolate Capsules usually available contain the equivalent of the following amounts of erythromycin: 125 and 250 mg.

CATEGORY and DOSE—See Erythromycin Estolate.

Erythromycin Estolate for Oral Suspension

Erythromycin Estolate for Oral Suspension is erythromycin estolate admixed with one or more suitable suspending and dispersing agents. It may contain one or more suitable colors, flavors, buffers, and preservatives. Erythromycin Estolate for Oral Suspension contains an amount of erythromycin estolate equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{37}H_{67}NO_{13}$ (erythromycin). Erythromycin Estolate for Oral Suspension conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Erythromycin Estolate for Oral Suspension in tight containers.

Sizes available—Erythromycin Estolate for Oral Suspension usually available contains the equivalent of the following amounts of erythromycin: 1.50 g. in 60-ml. containers and 3.75 g. in 150-ml. containers.

CATEGORY and DOSE—See Erythromycin Estolate.

Erythromycin Estolate Tablets

Erythromycin Estolate Tablets contain an amount of erythromycin estolate equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{37}H_{67}NO_{13}$ (erythromycin). Erythromycin Estolate Tablets conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

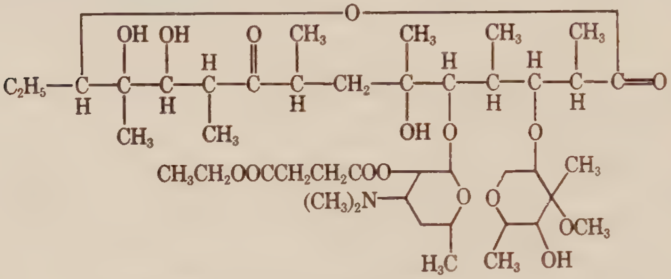
Packaging and storage—Preserve Erythromycin Estolate Tablets in tight containers.

Tablets available—Erythromycin Estolate Tablets usually available are chewable tablets and contain the equivalent of the following amount of erythromycin: 125 mg.

Labeling—Label Erythromycin Estolate Tablets to indicate that they are to be chewed before swallowing.

Category and Dose—See Erythromycin Estolate.

Erythromycin Ethylsuccinate*



Erythromycin 2′-(Ethyl Succinate)

$C_{43}H_{75}NO_{16}$ Mol. wt. 862.07

Erythromycin Ethylsuccinate contains the equivalent of not less than 76.5 percent of $C_{37}H_{67}NO_{13}$ (erythromycin base), calculated on the anhydrous basis. Erythromycin Ethylsuccinate conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Erythromycin Ethylsuccinate occurs as a white or slightly yellow, crystalline powder. It is odorless or practically odorless and is almost tasteless.

Solubility—Erythromycin Ethylsuccinate is freely soluble in alcohol, in chloroform, and in polyethylene glycol 400. It is very slightly soluble in water.

Packaging and storage—Preserve Erythromycin Ethylsuccinate in tight containers.

Category—Antibacterial.

Usual dose range—Intramuscular, **100 mg.** every 4 to 12 hours; oral, **1** to **2 g.** daily in divided doses.

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* Patented. See notice, page ii.

Erythromycin Ethylsuccinate Injection

Erythromycin Ethylsuccinate Injection is a sterile solution of erythromycin ethylsuccinate in polyethylene glycol 400. It contains erythromycin ethylsuccinate equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{37}H_{67}NO_{13}$ (erythromycin base). Erythromycin Ethylsuccinate Injection conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Erythromycin Ethylsuccinate Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injections available—Erythromycin Ethylsuccinate Injection usually available contains erythromycin ethylsuccinate equivalent to the following amounts of erythromycin base: 100 mg. in 2 ml.; 500 mg. in 10 ml.

Category and Dose—See Erythromycin Ethylsuccinate.

Erythromycin Ethylsuccinate for Oral Suspension

Erythromycin Ethylsuccinate for Oral Suspension is erythromycin ethylsuccinate admixed with one or more suitable suspending and dispersing agents. It may contain one or more suitable buffers, colors, flavors, and preservatives. It contains erythromycin ethylsuccinate equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{37}H_{67}NO_{13}$ (erythromycin base). Erythromycin Ethylsuccinate for Oral Suspension conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Erythromycin Ethylsuccinate for Oral Suspension in tight containers.

Sizes available—Erythromycin Ethylsuccinate for Oral Suspension usually available contains erythromycin ethylsuccinate equivalent to the following amounts of erythromycin base: 1.2 g. in a 30-ml. container; 2.4 g. in a 60-ml. container.

CATEGORY and DOSE—See Erythromycin Ethylsuccinate.

Erythromycin Ethylsuccinate Tablets

Erythromycin Ethylsuccinate Tablets contain erythromycin ethylsuccinate equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{37}H_{67}NO_{13}$ (erythromycin base). Erythromycin Ethylsuccinate Tablets conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

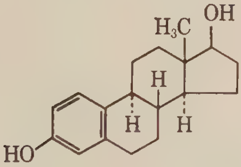
Packaging and storage—Preserve Erythromycin Ethylsuccinate Tablets in tight containers.

Tablets available—Erythromycin Ethylsuccinate Tablets usually available are chewable tablets and contain erythromycin ethylsuccinate equivalent to the following amount of erythromycin base: 200 mg

Labeling—Label Erythromycin Ethylsuccinate Tablets to indicate that they are to be chewed before swallowing.

CATEGORY and DOSE—See Erythromycin Ethylsuccinate.

Estradiol



Estra-1,3,5(10)-triene-3,17β-diol

$C_{18}H_{24}O_2$ Mol. wt. 272.39

Estradiol contains not less than 97.0 percent and not more than 103.0 percent of $C_{18}H_{24}O_2$, calculated on the dried basis.

Description—Estradiol occurs as white or creamy white, small crystals or as a crystalline powder. It is odorless, and is stable in air. It is hygroscopic.

Solubility—Estradiol is practically insoluble in water; it is soluble in alcohol, in acetone, in dioxane, in chloroform, and in solutions of fixed alkali hydroxides; it is sparingly soluble in vegetable oils.

Identification—Dissolve about 2 mg. of Estradiol in 2 ml. of sulfuric acid: the solution is greenish yellow and exhibits a green fluorescence. When the solution is diluted with 2 ml. of water, the color changes to pale orange. If 1 drop of ferric ammonium sulfate T.S. is added to the sulfuric acid solution before dilution with the water, the green color is strongly intensified, and after dilution with the water, the color is red.

Melting range, page 814—Estradiol melts between 173° and 179°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Estradiol, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Estradiol Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Estradiol in alcohol exhibits maxima and minima at the same wavelengths as that of NF Estradiol Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 280 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Estradiol, previously dried at 105° for 4 hours, determined in a solution in dioxane containing 100 mg. of Estradiol in each 10 ml., is between +76° and +83°.

Loss on drying, page 814—Dry Estradiol at 105° for 4 hours: it loses not more than 3.5 percent of its weight.

Limit of alpha-estradiol—Prepare a benzene solution of Estradiol, previously dried at 105° for 4 hours and accurately weighed, to contain about 50 mcg. in each ml. Prepare a similar solution of NF Estradiol Reference Standard. Transfer, in duplicate to separate 18 × 150-mm. test tubes, aliquots of the two solutions, each equivalent to 100 mcg. of Estradiol. Add a few small pieces of silicon carbide, or a few small glass beads to each tube, evaporate the solvent, and dry the residue over phosphorus pentoxide in a desiccator connected to a vacuum line for 1 hour.

To each tube and a blank tube, add 1.0 ml. of a reagent, prepared by mixing 1 volume of iron-phenol T.S. with 0.45 volume of water. Close the tubes with rubber finger stalls, and place in a boiling water bath for 2 minutes, shaking the tubes after 30 seconds for a few seconds without removing from the bath. Transfer to an ice bath for 2 minutes, then remove, add 4.0 ml. of dilute sulfuric acid (35 in 100), and mix thoroughly. Measure the absorbances of the solutions from the sample preparation (A_U) and the standard preparation (A_S) relative to the blank at 525 mμ and at 420 mμ, making any necessary correction for cell variation. Compare the relative amount of *alpha*-estradiol in the sample aliquot used by the following formula, $(A_{U525} - A_{U420}/2)/(A_{S525} - A_{S420}/2)$, in which A represents the absorbance at the indicated wavelength: the amount of *alpha*-estradiol in the sample preparation is not more than three times that in the NF Estradiol Reference Standard.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Estradiol Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Estradiol previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and ethyl acetate (6:1). Use 25.0 ml. of methanol, rather than dehydrated alcohol, to elute the steroid from the silica gel. Determine the absorbance at the maximum at about 281 mμ and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Estradiol taken: not more than 3 percent is found.

Assay—

Diluted iron-phenol solution—Just prior to use, dilute 10.0 ml. of iron-phenol T.S. to 100.0 ml. with dilute sulfuric acid (1 in 2), and shake vigorously.

Standard preparation—Weigh accurately about 50 mg. of NF Estradiol Reference Standard, dissolve it in sufficient ethyl acetate to make 100.0 ml., and mix. Transfer 4.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with ethyl acetate, and mix.

Assay preparation—Weigh accurately about 50 mg. of Estradiol, dissolve it in sufficient ethyl acetate to make 100.0 ml., and mix. Transfer 4.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with ethyl acetate, and mix.

Procedure—Pipet 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate glass-stoppered tubes, and evaporate each solution to dryness on a steam bath. Dry the residues in vacuum at 40° for 15 minutes, and cool in a desiccator. To each tube add 10.0 ml. of *Diluted iron-phenol solution* and add 20 ml. of *Diluted iron-phenol solution* to a third tube to serve as a blank. Stopper the tubes, shake vigorously at 5-minute intervals over a period of 30 minutes, then immerse the stoppered tubes above the level of their contents in a water bath, and heat the tubes at 65° to 70° in the bath for 1 hour. Cool the tubes in an ice-water bath, mix by inverting, and allow to stand at room temperature for 15 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 525 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{18}H_{24}O_2$ in the Estradiol taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Estradiol in well-closed, light-resistant containers.

CATEGORY—Estrogen.

USUAL DOSE RANGE—Implantation, **25 mg.** repeated when necessary; intramuscular, **220 mcg.** to **1.5 mg.** two or three times a week; oral, **200** to **500 mcg.** one to three times a day.

Estradiol Pellets

Estradiol Pellets are sterile pellets composed of estradiol in compressed form, without the presence of any binder, diluent, or excipient. They contain not less than 97.0 percent and not more than 103.0 percent of $C_{18}H_{24}O_2$.

Requirements—Estradiol Pellets meet the requirements under *Estradiol,* page 277, and under *Sterility Test for Solids,* page 874.

Solubility in chloroform—A solution of 25 mg. of Estradiol Pellets in 1 ml. of chloroform is clear and practically free from insoluble residue.

Weight variation—Weigh 5 Estradiol Pellets singly, and calculate the average weight. The average weight is not less than 95 percent and not more than 105 percent of the labeled weight of $C_{18}H_{24}O_2$, and each pellet weighs not less than 90 percent and not more than 110 percent of the labeled weight of $C_{18}H_{24}O_2$.

Assay—Proceed as directed in the *Assay* under *Estradiol,* page 277.

Packaging and storage—Preserve Estradiol Pellets in tight containers suitable for maintaining sterile contents holding one pellet each.

Pellets available—Estradiol Pellets usually available contain the following amount of estradiol: 25 mg.

CATEGORY and DOSE—See Estradiol.

Sterile Estradiol Suspension

Sterile Estradiol Suspension is a sterile suspension of estradiol in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{18}H_{24}O_2$.

Identification—Transfer a volume of well-mixed Sterile Estradiol Suspension, equivalent to about 10 mg. of estradiol, into a flask, make it acid to bromophenol blue T.S. with 1 *N* hydrochloric acid, mix thoroughly, and place in an ice bath for 15 minutes. Filter the acidified suspension with suction through a sintered-glass funnel. Wash the crystals of estradiol so isolated with five successive 5-ml. portions of water, and dry the funnel and contents to constant weight at 105°. The estradiol recovered meets the requirements for *Melting range* and for *Infrared absorption* under *Estradiol,* page 277.

Other requirements—Sterile Estradiol Suspension meets the requirements under *Injections,* page 810.

Assay—

Diluted iron-phenol solution and *Standard preparation*—Prepare as directed in the *Assay* under *Estradiol,* page 277.

Assay preparation—Transfer an accurately measured volume of Sterile Estradiol Suspension, equivalent to about 2 mg. of estradiol, to a 125-ml. separator containing 25 ml. of water, and extract with four 50-ml. portions and one 30-ml. portion of ethyl acetate. Filter each extract through ethyl acetate-washed cotton (layered over with anhydrous sodium sulfate) into a 500-ml. volumetric flask, dilute to volume with ethyl acetate, and mix.

Procedure—Pipet 5.0 ml. of the *Standard preparation* and 25 ml. of the *Assay preparation* into separate glass-stoppered tubes, and continue as directed for *Procedure* in the *Assay* under *Estradiol,* page 277, beginning with "... evaporate each solution to dryness on a steam bath." Calculate the quantity, in mg., of $C_{18}H_{24}O_2$ in each ml. of the Suspension taken by the formula $0.1 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and *V* is the volume, in ml., of the Suspension taken.

Packaging and storage—Preserve Sterile Estradiol Suspension in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Sterile Estradiol Suspension usually available contains the following amounts of estradiol: 250 mcg. in 1 ml.; 1 mg. in 1 ml.; 2.5 mg. in 10 ml.; 2.2 mg. in 10 ml.; 4.4 mg. in 10 ml.; 11 mg. in 10 ml.; 5.5 mg. in 25 ml.

CATEGORY and DOSE—See Estradiol.

Estradiol Tablets

Estradiol Tablets contain not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{18}H_{24}O_2$.

Disintegration, page 878—The disintegration time limit for Estradiol Tablets is 15 minutes.

Content uniformity, *Method I,* page 799—Estradiol Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Diluted iron-phenol solution and *Standard preparation*—Prepare as directed in the *Assay* under *Estradiol,* page 277.

Assay preparation—Weigh and finely powder not less than 20 Estradiol Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mcg. of estradiol, and transfer to a 125-ml. separator containing 25 ml. of water, and extract with five 45-ml. portions of ethyl acetate. Filter each extract through ethyl acetate-washed cotton (layered over with anhydrous sodium sulfate) into a 250-ml. volumetric flask, dilute to volume with ethyl acetate, and mix.

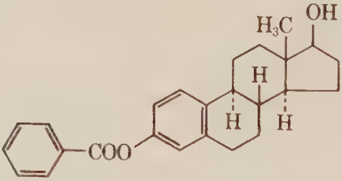
Procedure—Pipet 5.0 ml. of the *Standard preparation* and 50.0 ml. of the *Assay preparation* into separate glass-stoppered tubes, and continue as directed for *Procedure* in the *Assay* under *Estradiol,* page 277, beginning with "... evaporate each solution to dryness on a steam bath." Calculate the quantity, in mg., of $C_{18}H_{24}O_2$ in the portion of the Tablets taken by the formula $0.025C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Estradiol Tablets in well-closed containers.

Tablets available—Estradiol Tablets usually available contain the following amounts of estradiol: 200 and 500 mcg.

CATEGORY and DOSE—See Estradiol.

Estradiol Benzoate



Estradiol 3-Benzoate

$C_{25}H_{23}O_3$ Mol. wt. 376.50

Estradiol Benzoate contains not less than 97.0 percent and not more than 103.0 percent of $C_{25}H_{28}O_3$, calculated on the dried basis.

Description—Estradiol Benzoate occurs as a white or creamy white, crystalline powder. It is odorless, and is stable in air.

Solubility—Estradiol Benzoate is practically insoluble in water. It is soluble in alcohol, in acetone, in benzene, and in dioxane. It is slightly soluble in ether, and sparingly soluble in vegetable oils.

Identification—Prepare a solution of Estradiol Benzoate in benzene containing 5 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a benzene solution of NF Estradiol Benzoate Reference Standard containing 5 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of benzene and ethyl acetate (6:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by spraying with a solution of vanillin and sulfuric acid in acetic acid (prepared by dissolving 1 g. of vanillin and 2 ml. of sulfuric acid in 98 ml. of acetic acid) and by heating at 100° for 10 minutes: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution, and the presence, size, and intensity of any secondary spots obtained from the sample solution do not exceed similar spots obtained from the Reference Standard solution.

Melting range, *Class Ia,* page 815—Estradiol Benzoate melts between 190° and 196°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Estradiol Benzoate, previously dried over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Estradiol Benzoate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 10,000 solution of Estradiol Benzoate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Estradiol Benzoate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 230 mμ, do not differ by more than 5 percent.

Specific rotation, page 822—The specific rotation of Estradiol Benzoate, previously dried over silica gel for 4 hours, determined in a solution in dioxane containing 100 mg. of Estradiol Benzoate in each 10 ml., is between +57° and +62°.

Loss on drying, page 814—Dry Estradiol Benzoate over silica gel for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 100 mg. of Estradiol Benzoate is negligible.

Completeness and reaction of solution—Dissolve 100 mg. of Estradiol Benzoate in 5 ml. of warm alcohol: no insoluble residue remains and the solution after cooling is only slightly acid to litmus.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Estradiol Benzoate Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Estradiol Benzoate previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of benzene and ethyl acetate (6:1). Use 25.0 ml. of methanol, rather than dehydrated alcohol, to elute the steroid from the silica gel. Determine the absorbance at the maximum at about 229 mμ and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Estradiol Benzoate taken: not more than 3 percent is found.

Assay—

Chromatographic column—Pack a pledget of glass wool in the base of an 18 × 300-mm. chromatographic tube having a 10-mm. stem extending about 100 mm. below an unlubricated stopcock. Arrange a long-stemmed, glass-stoppered 500-ml. separator to serve as a reservoir for maintaining a constant level of liquid in the tube. Transfer about 22 g. of dry silica gel G (10 to 30-μ particle size) to the tube, and pack the column by applying vacuum to the delivery tip. Adjust the column height to about 190 mm.

Mobile solvent—Mix 365 ml. of benzene with 50 ml. of ethyl acetate.

Diluted iron-phenol solution—Just prior to use, dilute 1 volume of iron-phenol T.S. to 10 volumes with a cool solution of 45 volumes of sulfuric acid in 55 volumes of water. Mix, and dispense from a small-bore buret, arranged to exclude moisture.

Standard preparation—Transfer about 50 mg. of NF Estradiol Benzoate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add dehydrated alcohol to volume, and mix. Transfer 2.0 ml. of this solution to a 50-ml. conical flask, and continue as directed under *Assay preparation* beginning with "... add 10 ml. of 0.1 *N* sodium hydroxide."

Assay preparation—Transfer about 10 mg. of Estradiol Benzoate, accurately weighed, to a 50-ml. volumetric flask, add *Mobile solvent* to volume, and mix. Slowly pipet 5.0 ml. of this solution onto the chromatographic column. (Note—At no time during the development of the chromatogram should the surface of the column be free of solvent.) Allow all but a 3-mm. layer of the solution to absorb into the column, then add 5 ml. of the *Mobile solvent,* and apply vacuum. Draw all but 3 mm. into the column, add 5 ml. more of the *Mobile solvent,* and again draw all but 3 mm. into the column. Pass 160 ml. of the *Mobile solvent* into the column. Withdraw and discard the first 47 ml. of eluate. Collect the next 100 ml. of eluate in two separate portions of 50 ml. each. Evaporate the first portion to dryness in a 50-ml. glass-stoppered conical flask on a steam bath with the aid of a current of air. Add the second 50-ml. portion to the same flask, and evaporate to dryness in the same manner. Dissolve the residue in 2.0 ml. of dehydrated alcohol, add 10 ml. of 0.1 *N* sodium hydroxide, mix, and heat in a water bath at 60° for 30 minutes. Cool, and transfer with the aid of two 10-ml. portions of 0.1 *N* sodium hydroxide to a 250-ml. separator. Cautiously add 10 ml. of cold dilute sulfuric acid (1 in 2), mix, and extract with 20 ml. of benzene. Dry the extract over 1 g. of anhydrous sodium sulfate, then transfer to a 50-ml. volumetric flask. Repeat the extraction with two 15-ml. portions of benzene, drying each extract over the same anhydrous sodium sulfate, and transfer to the volumetric flask. Dilute to volume with benzene, and mix.

Procedure—Transfer 5.0 ml. of each of the *Standard preparation* and of the *Assay preparation* to separate 50-ml. glass-stoppered test tubes, and evaporate to dryness on a steam bath with the aid of a stream of nitrogen. Wipe dry the exterior of the tubes, then dry the residues in vacuum at 40° for 15 minutes, and cool in a desiccator. Pipet 10.0 ml. of *Diluted iron-phenol solution* into each tube and into a third tube to serve as the blank, stopper the tubes, and shake vigorously at 5-minute intervals over a period of 30 minutes. Heat the solutions in a boiling water bath for 60 minutes, chill rapidly to room temperature in an ice-water bath, and then swirl the tubes in water at room temperature for several minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 525 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{25}H_{28}O_3$ in the Estradiol Benzoate taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Estradiol Benzoate in well-closed, light-resistant containers.

CATEGORY—Estrogen.

USUAL DOSE RANGE—Intramuscular, initial, **1.0** to **1.66 mg.** two or three times a week for 2 or 3 weeks; maintenance, **330 mcg.** to **1.0 mg.** twice weekly.

Estradiol Benzoate Injection

Estradiol Benzoate Injection is a sterile solution of estradiol benzoate in a suitable oil. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{25}H_{28}O_3$.

Identification—On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 40 μl. each of the *Assay preparation* and of the *Standard preparation* prepared as directed in the *Assay*. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of benzene and ethyl acetate (6:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots by viewing the plate under shortwave ultraviolet light: the R_f value of the main spot obtained from the *Assay preparation* corresponds to that obtained from the *Standard preparation*.

Other requirements—Estradiol Benzoate Injection meets the requirements under *Injections*, page 810.

Assay—

Chromatographic column, Mobile solvent, Diluted iron-phenol solution, and *Standard preparation*—Prepare as directed in the *Assay* under *Estradiol Benzoate*, page 280.

Assay preparation—Transfer an accurately measured volume of Estradiol Benzoate Injection, equivalent to about 10 mg. of estradiol benzoate, to a 50-ml. volumetric flask, add *Mobile solvent* to volume, and mix. (NOTE—If the concentration of estradiol benzoate is less than 1 mg. per ml., use 10.0 ml. of the Injection as the sample.) Continue as directed for *Assay preparation* in the *Assay* under *Estradiol Benzoate*, page 280, beginning with "Slowly pipet 5.0 ml. of this solution onto the chromatographic column."

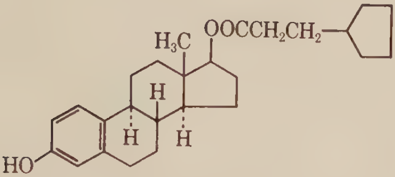
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Estradiol Benzoate*, page 280. Calculate the quantity, in mg., of $C_{25}H_{28}O_3$ in each ml. of the Injection taken by the formula $0.5 \times (C/V) \times (A_U/A_S)$, in which V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Estradiol Benzoate Injection in single-dose or in multiple-dose containers, preferably of Type I or Type III glass.

Injections available—Estradiol Benzoate Injection usually available contains the following amounts of estradiol benzoate: 10 and 33.3 mg. in 10 ml.

CATEGORY and DOSE—See Estradiol Benzoate.

Estradiol Cypionate*



Estradiol 17-Cyclopentanepropionate

$C_{26}H_{36}O_3$ Mol. wt. 396.58

Estradiol Cypionate contains not less than 97.0 percent and not more than 103.0 percent of $C_{26}H_{36}O_3$, calculated on the dried basis.

Description—Estradiol Cypionate is a white to practically white, crystalline powder. It is odorless or has a slight odor.

Solubility—Estradiol Cypionate is insoluble in water. It is soluble in alcohol, in acetone, in chloroform, and in dioxane. It is sparingly soluble in vegetable oils.

Identification—

A: Dissolve about 2 mg. of Estradiol Cypionate in 2 ml. of sulfuric acid: the solution is greenish yellow and exhibits a green fluorescence.

B: Transfer 5 mg. of Estradiol Cypionate to a small beaker, add 5 ml. of potassium hydroxide solution (1 in 10), and heat on a steam bath for 15 minutes. Mix 50 mg. of sulfanilic acid with 2 ml. of diluted hydrochloric acid, warm the mixture, then cool it in ice water, and slowly add, with agitation, 0.3 ml. of a solution of sodium nitrite (1 in 10). Add this solution to the saponified Estradiol Cypionate: a red color is produced.

Melting range, page 814—Estradiol Cypionate melts between 149° and 153°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Estradiol Cypionate, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Estradiol Cypionate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 10,000 solution of Estradiol Cypionate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Estradiol Cypionate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 280 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Estradiol Cypionate, calculated on the dried basis, determined in a solution in dioxane containing 200 mg. of Estradiol Cypionate in each 10 ml., is between +39° and +44°.

Loss on drying, page 814—Dry Estradiol Cypionate at 105° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Estradiol Cypionate yields not more than 0.2 percent of residue on ignition.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Estradiol Cypionate Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Estradiol Cypionate previously dried at 105° for 4 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and acetone (4:1), and determining the absorbance at the maximum at about 280 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Estradiol Cypionate taken: not more than 3 percent is found.

Assay—

Diluted iron-phenol solution—Just prior to use, dilute 10.0 ml. of iron-phenol T.S. to 100.0 ml. with dilute sulfuric acid (2 in 3), and shake vigorously.

Standard preparation—Weigh accurately about 25 mg. of NF Estradiol Cypionate Reference Standard, dissolve it in sufficient alcohol to make 100.0 ml., and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix.

Assay preparation—Weigh accurately about 25 mg. of Estradiol Cypionate, dissolve it in sufficient alcohol to make 100.0 ml., and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix.

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* Patented. See notice, page ii.

Procedure—Pipet 4.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate glass-stoppered tubes, and evaporate each solution to dryness in a stream of air with the aid of gentle heat. Pipet 1.0 ml. of alcohol into each tube and into a third glass-stoppered tube to serve as the blank. Add 10.0 ml. of *Diluted iron-phenol solution* to each tube, stopper, and mix vigorously. Immerse the stoppered tubes above the level of their contents in a water bath, and heat in the bath at 75° to 80° for 2 hours. Cool the tubes in ice water, mix by inverting, and allow to stand at room temperature for 15 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 510 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{26}H_{36}O_3$ in the portion of Estradiol Cypionate taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Estradiol Cypionate in tight, light-resistant containers.

CATEGORY—Estrogen.

USUAL DOSE RANGE—Intramuscular, initial, **1** to **5 mg.** weekly for 2 to 3 weeks; maintenance, **2** to **5 mg.** every 3 to 4 weeks.

Estradiol Cypionate Injection

Estradiol Cypionate Injection is a sterile solution of estradiol cypionate in a suitable oil. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{26}H_{36}O_3$.

Identification—Transfer an amount of Estradiol Cypionate Injection, equivalent to 5 mg. of estradiol cypionate, to a 50-ml. glass-stoppered test tube, and add 30 ml. of alcohol. Shake the mixture vigorously for 5 minutes, centrifuge until the two layers have separated, and transfer the alcohol layer, with the aid of a hypodermic syringe, to a 50-ml. beaker. Evaporate to dryness on a steam bath, add 5 ml. of potassium hydroxide solution (1 in 10), and heat on a steam bath for 15 minutes. Mix 50 mg. of sulfanilic acid with 2 ml. of diluted hydrochloric acid, warm the mixture, then cool it in ice water, and slowly add, with agitation, 0.3 ml. of a solution of sodium nitrite (1 in 10). Add this solution to the saponified estradiol cypionate: a red color is produced.

Other requirements—Estradiol Cypionate Injection meets the requirements under *Injections*, page 810.

Assay—

Diluted iron-phenol solution and *Standard preparation*—Prepare as directed in the *Assay* under *Estradiol Cypionate*, page 283.

Assay preparation—Transfer an accurately measured volume of Estradiol Cypionate Injection, equivalent to about 2.5 mg. of estradiol cypionate, to a 125-ml. separator containing 50 ml. of dilute alcohol (9 in 10), and shake well. Add 40 ml. of solvent hexane, shake, and collect the alcohol phase in a 250-ml. separator containing 25 ml. of solvent hexane. Extract the solvent hexane remaining in the first separator with two successive 25-ml. portions of dilute alcohol (9 in 10), and add each alcohol extract to the second separator. Shake the second separator, and filter the alcohol phase through paper into a 200-ml. volumetric flask. Extract the solvent hexane layer with 10 ml. of dilute alcohol (9 in 10), filter through the same paper into the 200-ml. volumetric flask, dilute to volume with alcohol, and mix.

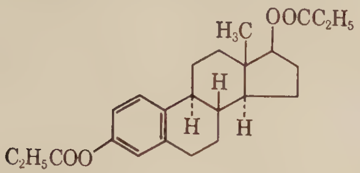
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Estradiol Cypionate*, page 283. Calculate the quantity, in mg., of $C_{26}H_{36}O_3$ in each ml. of the Injection taken by the formula $0.2 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Estradiol Cypionate Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Estradiol Cypionate Injection usually available contains the following amounts of estradiol cypionate: 10 mg. in 10 ml.; 25 mg. in 5 ml.; 50 mg. in 10 ml.

CATEGORY and DOSE—See Estradiol Cypionate.

Estradiol Dipropionate



$C_{24}H_{32}O_4$ Mol. wt. 384.52

Estradiol Dipropionate contains not less than 97.0 percent and not more than 103.0 percent of $C_{24}H_{32}O_4$, calculated on the dried basis.

Description—Estradiol Dipropionate occurs as small, white or slightly off-white crystals or crystalline powder.

Solubility—Estradiol Dipropionate is practically insoluble in water. It is soluble in acetone and in alcohol, and is sparingly soluble in vegetable oils.

Identification—

A: Dissolve about 100 mg. of Estradiol Dipropionate in 10 ml. of methanol, add a solution of 150 mg. of potassium carbonate in 0.5 ml. of water, and reflux on a steam bath for 4 hours. At the end of this period add 30 ml. of water, and gently evaporate to about 15 ml. Cool, add 15 ml. of water, and keep the mixture between 5° and 10° for 1 hour. Filter the precipitate with suction, wash it with cold water until the last washing is neutral to litmus, and dry at 105°: the estradiol so obtained melts between 173° and 179°, page 814.

B: Dissolve about 2 mg. of the estradiol obtained in *Identification test A* in 2 ml. of sulfuric acid: the solution is greenish yellow and exhibits a green fluorescence Add to the solution 1 drop of ferric ammonium sulfate T.S.: the green color is strongly intensified, and on dilution with water the color changes to red or orange-red.

Melting range, *Class Ia,* page 814—Estradiol Dipropionate melts between 104° and 109°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Estradiol Dipropionate, previously dried in vacuum over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Estradiol Dipropionate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 5000 solution of Estradiol Dipropionate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Estradiol Dipropionate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 268 $m\mu$, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Estradiol Dipropionate, previously dried in vacuum over silica gel for 4 hours, determined in a solution in dioxane containing 100 mg. of Estradiol Dipropionate in each 10 ml., is between +36° and +40°.

Loss on drying, page 814—Dry Estradiol Dipropionate in vacuum over silica gel for 4 hours: it loses not more than 0.5 percent of its weight.

Completeness and reaction of solution—Dissolve 100 mg. of Estradiol Dipropionate in 5 ml. of warm alcohol: no insoluble residue remains and the solution after cooling is only slightly acid to litmus.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Estradiol Dipropionate Reference Standard, previously dried in vacuum over silica gel for 4 hours, to prepare a solution containing approximately 20 mg. per ml.

Test preparation—Weigh accurately about 100 mg. of Estradiol Dipropionate, previously dried in vacuum over silica gel for 4 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 5.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of benzene and acetone (4:1), and determining the absorbance at the maximum at about 268 $m\mu$. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 5 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Estradiol Dipropionate taken: not more than 3 percent is found.

Assay—

Standard preparation—Weigh accurately about 50 mg. of NF Estradiol Dipropionate Reference Standard, dissolve it in sufficient methanol to make 50.0 ml., and mix.

Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 0.1 *N* sodium hydroxide, and mix.

Assay preparation—Transfer to a 40-ml. centrifuge tube 5.0 ml. of a 1 in 10 solution of sodium hydroxide in 80 percent methanol, then transfer to the tube 5.0 mg. of Estradiol Dipropionate, and shake mechanically for 15 minutes. Add 20 ml. of solvent hexane and 5 ml. of sodium hydroxide solution (1 in 10), shake for 2 minutes, and centrifuge. Remove the lower layer, and filter it through cotton into a 50-ml. volumetric flask. Add 10 ml. of sodium hydroxide solution (1 in 10) to the centrifuge tube, shake for 2 minutes, centrifuge, and add the lower layer to the volumetric flask. Carefully add, dropwise, cooled dilute sulfuric acid (1 in 2) until the solution is neutral to indicator paper, dilute to volume with 0.1 *N* sodium hydroxide, and mix. The solution may be slightly turbid.

Procedure—Into each of three 10-ml. volumetric flasks pipet 1.0 ml. of a 1 in 500 solution of NF 4-Amino-6-chloro-1,3-benzenedisulfonamide Reference Standard in methanol, 1.0 ml. of sodium nitrite solution (1 in 100), and 1.0 ml. of 1 *N* hydrochloric acid. Mix, and allow to stand for 2 minutes. Pipet 2.0 ml. of the *Standard preparation* into the first flask, 2.0 ml. of the *Assay preparation* into the second flask, and 2.0 ml. of water into the third flask to serve as the blank. To each flask add 2.0 ml. of 2 *N* sodium acetate, mix, and allow to stand for exactly 5 minutes. Dilute each flask to volume with 1 *N* sodium hydroxide, mix, and filter the solutions through a small medium-porosity sintered-glass funnel. Concomitantly determine the absorbances of the filtrates in 1-cm. cells, at the maximum at about 500 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{24}H_{32}O_4$ in the Estradiol Dipropionate taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Estradiol Dipropionate in well-closed, light-resistant containers.

CATEGORY—Estrogen.

USUAL DOSE RANGE—Intramuscular, initial, **1 to 5 mg.** every 1 to 2 weeks; maintenance, **1 to 2.5 mg.** every 10 days to 2 weeks.

Estradiol Dipropionate Injection

Estradiol Dipropionate Injection is a sterile solution of estradiol dipropionate in a suitable oil. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{32}O_4$.

Identification—Line the inside of a chromatographic chamber suitable for descending chromatography (see page 798) with filter paper (Whatman No. 1 or equivalent). Fill the solvent trough with *n*-heptane to serve as the mobile phase, and also place sufficient of the same liquid on the bottom of the chamber to permit the liner to be in contact with it. Allow the chamber to equilibrate overnight. Prepare a strip of filter paper, about 10 × 45 cm., draw a line across the narrow dimension about 6 cm. from one end, and mark two points for application of solutions along this line about 2.5 cm. from each edge of the paper. Immerse the paper in a 1 in 10 solution of 2-phenoxyethanol in acetone, and air-dry at room temperature for about 30 minutes. With a micropipet streak, over a distance of 1 to 2 cm., a volume of Injection equivalent to 25 mcg. of estradiol dipropionate at one application point, and similarly streak a solution equivalent to 25 mcg. of NF Estradiol Dipropionate Reference Standard, in equal volumes of chloroform and methanol, at the other application point. Suspend the strip in the chamber, and allow to develop for 90 minutes. Remove the strip, mark the solvent front, and dry the strip in an oven at 60° for 3 hours. Spray the strip with a 1 in 10 solution of phosphomolybdic acid in dehydrated alcohol, and heat the strip at 90° to 100° for several minutes. A blue spot on a bluish yellow background is produced by the sample at the same distance (R_f approximately 0.22) from the point of application as that produced by the standard. Other spots may be produced by the oil vehicle. Estradiol and ethinyl estradiol remain at the origin.

Other requirements—Estradiol Dipropionate Injection meets the requirements under *Injections*, page 810.

Assay—

Standard preparation—Prepare as directed in the *Assay* under ***Estradiol Dipropionate***, page 285.

Assay preparation—Transfer to a 40-ml. centrifuge tube 5.0 ml. of a 1 in 10 solution of sodium hydroxide in 80 percent methanol, then transfer to the tube an accurately measured volume of Estradiol Dipropionate Injection, equivalent to about 5 mg. of estradiol dipropionate, and continue as directed for *Assay preparation* in the *Assay* under *Estradiol Dipropionate,* page 285, beginning with "... and shake mechanically for 15 minutes."

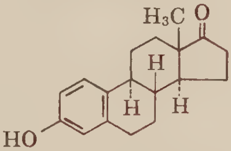
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Estradiol Dipropionate,* page 285. Calculate the quantity, in mg., of $C_{24}H_{32}O_4$ in each ml. of the Injection taken by the formula $0.05 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation,* and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Estradiol Dipropionate Injection in single-dose or in multiple-dose containers, preferably of Type I or Type III glass.

Injections available—Estradiol Dipropionate Injection usually available contains the following amounts of estradiol dipropionate: 2.5 mg. in 1 ml.; 10 and 50 mg. in 10 ml.

CATEGORY and DOSE—See Estradiol Dipropionate.

Estrone



3-Hydroxyestra-1,3,5(10)-trien-17-one

$C_{18}H_{22}O_2$ Mol. wt. 270.37

Estrone contains not less than 97.0 percent and not more than 103.0 percent of $C_{18}H_{22}O_2$.

Description—Estrone occurs as small, white crystals, or as a white to creamy white, crystalline powder. It is odorless, and is stable in air.

Solubility—Estrone is practically insoluble in water. It is soluble in alcohol, in acetone, in dioxane, and in vegetable oils. It is slightly soluble in solutions of fixed alkali hydroxides.

Melting range, *Class Ia,* page 815—Estrone melts between 256° and 262°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Estrone exhibits maxima only at the same wavelengths as that of NF Estrone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—Prepare a 1 in 20,000 solution of Estrone in alcohol by heating on a steam bath and cooling to room temperature. The solution exhibits maxima and minima at the same wavelengths as that of NF Estrone Reference Standard, similarly measured.

Clarity of solution—Add 100 mg. of Estrone to 100 ml. of sodium hydroxide T.S. in a 125-ml. conical flask, and heat on a steam bath until solution is complete, then cool, and transfer to a 100-ml. color-comparison tube: the solution is clear.

Specific rotation, page 822—The specific rotation of Estrone, determined in a solution in dioxane containing 100 mg. of Estrone in each 10 ml., is between +158° and +165°.

Residue on ignition, page 858—The residue on ignition from 100 mg. of Estrone is negligible.

Equilenin and equilin—Dissolve 10 mg. of Estrone in sufficient alcohol to make 50 ml. Transfer 5 ml. of the solution to a small beaker. Add 5 ml. of a buffer solution prepared by dissolving 2 ml. of glacial acetic acid and 13.3 g. of anhydrous sodium acetate in water to make 100 ml., warm to about 50°, and add 1 ml. of a freshly prepared 1 in 200 solution of 2,6-dibromoquinone-chlorimide in alcohol. Mix, and allow to stand for 30 minutes. Transfer the solution to a small separator, add 10 ml. of chloroform and 20 ml. of sodium hydroxide T.S., and shake vigorously for 2 minutes. Separate the chloroform layer, and filter rapidly through a dry filter paper into a dry test tube, rejecting the first 2 ml. of the filtrate. Viewed transversely against a white background, the chloroform filtrate shows no more red color than that produced by similarly treating 5 ml. of an alcohol solution containing 20 mcg. of equilenin.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Estrone Reference Standard to prepare a solution containing approximately 5 mg. per ml.

Test preparation—Weigh accurately about 50 mg. of Estrone, previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Pro-*

cedure under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and acetone (4:1), and determining the absorbance at the maximum at about 280 mμ. Calculate the percentage of chromatographic impurities by the formula 100 − [100 × 10 × (C/W) × (A_U/A_S)], in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Estrone taken: not more than 3 percent is found.

Assay—Transfer about 50 mg. of Estrone, accurately weighed, to a 100-ml. volumetric flask, add 50 ml. of alcohol, dissolve by heating on a steam bath, and cool. Dilute to volume with alcohol, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Estrone Reference Standard, in the same medium at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 280 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{18}H_{22}O_2$ in the Estrone taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Estrone in tight, light-resistant containers.

CATEGORY—Estrogen.

USUAL DOSE—Intramuscular, **1 mg.** one or more times a week as required; reduce to maintenance dose as soon as response is obtained.

USUAL DOSE RANGE—**200 mcg.** to **5 mg.** per week.

Estrone Injection

Estrone Injection is a sterile solution of estrone in a suitable oil. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{18}H_{22}O_2$.

Identification—Dissolve the residue obtained in the *Assay* in sufficient alcohol to make a solution containing 0.5 mg. of estrone in each ml. Transfer to an acetylation flask, and evaporate to dryness. Add 10 mg. of hydroxylamine hydrochloride, 0.2 ml. of glacial acetic acid, and 5 ml. of alcohol, and reflux for 5 hours. Dilute with 5 ml. of water, filter, and recrystallize the precipitate from hot alcohol: the estrone oxime so obtained melts between 236° and 242°, page 814.

Other requirements—Estrone Injection meets the requirements under *Injections*, page 810.

Assay—[NOTE: Use only water as a lubricant for the separators used in this assay, and complete the assay without interruption other than at the stage of obtaining the dry residue from the ether extract.] Pipet a volume of Estrone Injection, equivalent to about 10 mg. of estrone, into a suitable separator containing 25 ml., or not less than twice the volume of the Injection taken, of solvent hexane. Add 10 ml. of sodium hydroxide solution (1 in 10), shake vigorously for 2 minutes, and allow to separate completely. Transfer the aqueous layer to a second 125-ml. separator, and repeat the extraction of the solvent hexane with two additional, successive 10-ml. portions of the sodium hydroxide solution, adding each extract to the second separator. Complete the alkaline extraction as quickly as possible, since long standing in strongly alkaline solution may cause decomposition of the estrone. Wash the combined alkaline extracts with 25 ml. of solvent hexane. Using dilute sulfuric acid (1 in 2), acidify the combined alkaline extracts until acid to litmus. Cool thoroughly, add 25 ml. of benzene, shake carefully for 1 minute, and allow to separate. Transfer the acid layer to another 125-ml. separator, and extract with a second 25-ml. portion of benzene. Discard the acid layer. Extract the benzene layers with two 5-ml. portions of sodium carbonate T.S. and two 5-ml. portions of water. Discard the water layers. Transfer the benzene solutions to a beaker with the aid of benzene, and evaporate on a steam bath, with the aid of a current of air, to dryness.

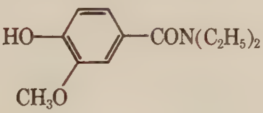
Dissolve the residue from the benzene extract in a small quantity of chloroform, warming, if necessary, and completely transfer the solution, with the aid of a few ml. of chloroform, to a 20 × 150-mm. test tube. Carefully evaporate the chloroform on a steam bath with the aid of a current of air. Add 100 mg. of trimethylacethydrazide ammonium chloride and 0.5 ml. of glacial acetic acid to the test tube, stopper loosely, and heat in a boiling water bath for 5 minutes. Cool the reaction mixture in an ice bath, dissolve it in a small volume of cold water, and completely transfer it, with the aid of a small volume of water, to a 125-ml. separator containing 25 ml. of cold water. Neutralize the solution to litmus paper with sodium hydroxide T.S. (approximately 6 ml.), and wash at once with three successive 15-ml. portions of chloroform. Combine the chloroform washings in another separator, and wash them with 5 ml. of water. Discard the chloroform, and add the wash water to the first separator. Add 2 ml. of dilute sulfuric acid (1 in 2), and allow to remain at room temperature for 2 hours. Add 15 ml. of chloroform, shake vigorously for 1 minute, and allow to separate. Transfer the chloroform layer to another separator, and repeat the extraction of the water layer with three additional, successive 15-ml. portions of chloroform. Wash the combined chloroform extracts with 5 ml. of water, filter through chloroform-washed cotton into a beaker, evaporate to a small volume, and transfer completely, with the aid of several small portions of chloroform, to a tared 25-ml. beaker. Evaporate on a steam bath, with the aid of a current of air, to dryness, and dry the residue of estrone in a vacuum desiccator to constant weight: the weight of the residue, corrected for the residue of a reagent blank following the above procedure, indicates the amount of $C_{18}H_{22}O_2$ in the volume of the Injection taken.

Packaging and storage—Preserve Estrone Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injections available—Estrone Injection usually available contains the following amounts of estrone: 200 and 500 mcg. and 1 mg. in 1 ml.; 10 mg. in 10 ml.

CATEGORY and DOSE—See Estrone.

Ethamivan*



N,*N*-Diethylvanillamide

$C_{12}H_{17}NO_3$ Mol. wt. 223.27

Ethamivan contains not less than 98.0 percent and not more than 102.0 percent of $C_{12}H_{17}NO_3$, calculated on the dried basis.

Description—Ethamivan occurs as a white or practically white, crystalline powder having a faint, characteristic odor.

Solubility—Ethamivan is sparingly soluble in water and in ether. It is very soluble in chloroform and freely soluble in alcohol, in acetone, and in benzene.

Identification—

A: Dissolve about 100 mg. of Ethamivan in 5 ml. of water, and add 3 drops of ferric chloride T.S.: a blue color is produced.

B: Dissolve about 500 mg. of Ethamivan in 4 ml. of dilute sulfuric acid (1 in 4), boil for several minutes, and cool. Make the solution alkaline with a sodium hydroxide T.S., and heat over a gentle flame: a typical amine odor develops and the vapors turn red litmus blue.

Melting range, page 814—Ethamivan melts between 94° and 97°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Ethamivan, previously dried over phosphorus pentoxide for 24 hours, exhibits maxima only at the same wavelengths as that of NF Ethamivan Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 25,000 solution of Ethamivan in methanol exhibits maxima and minima at the same wavelengths as that of NF Ethamivan Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 281 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Ethamivan (1 in 100) is between 5.5 and 7.0.

Loss on drying, page 814—Dry Ethamivan in a desiccator over phosphorus pentoxide for 24 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Ethamivan yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Ethamivan is 10 parts per million.

Assay—

Standard preparation—Transfer about 25 mg. of NF Ethamivan Reference Standard, accurately weighed, to a 250-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer about 25 mg. of Ethamivan, accurately weighed, to a 250-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with water, and mix.

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* Patented. See notice, page ii.

Procedure—Transfer 5.0 ml. of the *Standard preparation*, of the *Assay preparation*, and of water to separate test tubes. To each tube add 3.0 ml. of diluted (1 in 4) Folin-Ciocalteu phenol T.S. and 10.0 ml. of sodium carbonate solution (1 in 7), mix, and allow to stand for 15 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 660 $m\mu$, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{12}H_{17}NO_3$ in the Ethamivan taken by the formula $1.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Ethamivan in well-closed, light-resistant containers.

CATEGORY—Central and respiratory stimulant.

USUAL DOSE RANGE—Intravenous, **0.5 to 5 mg. per kg.** of body weight, given slowly as a single injection; and then may follow with continuous intravenous infusion at the rate of 10 mg. per minute as determined by response of the patient.

Ethamivan Injection

Ethamivan Injection is a sterile solution of ethamivan in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{12}H_{17}NO_3$.

Identification—To 2 drops of Ethamivan Injection add 2 drops of a freshly prepared solution consisting of equal parts of sodium nitrite solution (1 in 20) and sulfanilic acid solution (1 in 10) in diluted hydrochloric acid: an orange color is produced.

Pyrogen—Ethamivan Injection meets the requirements of the *Pyrogen Test*, page 851, the test dose being 0.1 ml. per kg. of a solution containing 50 mg. of ethamivan in each ml.

pH, page 824—The pH of Ethamivan Injection is between 9.3 and 9.6.

Other requirements—Ethamivan Injection meets the requirements under *Injections*, page 810.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Ethamivan*, page 289.

Assay preparation—Transfer an accurately measured volume of Ethamivan Injection, equivalent to about 50 mg. of ethamivan, to a 100-ml. volumetric flask, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with water, and mix.

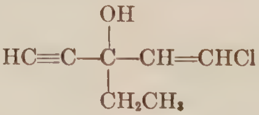
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Ethamivan*, page 289. Calculate the quantity, in mg., of $C_{12}H_{17}NO_3$ in each ml. of the Injection taken by the formula $2.5 \times (C/V) \times (A_U/A_S)$, in which V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Ethamivan Injection in single-dose or multiple-dose containers, preferably of Type I glass, protected from light.

Injections available—Ethamivan Injection usually available contains the following amounts of ethamivan: 100 mg. in 2 ml.; 500 mg. in 10 ml.

CATEGORY and DOSE—See Ethamivan.

Ethchlorvynol*



$$HC\equiv C-\overset{OH}{\underset{CH_2CH_3}{C}}-CH=CHCl$$

1-Chloro-3-ethyl-1-penten-4-yn-3-ol

C_7H_9ClO Mol. wt. 144.60

Ethchlorvynol contains not less than 95.0 percent and not more than 102.0 percent of C_7H_9ClO, calculated on the anhydrous basis.

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* Patented. See notice, page ii.

Description—Ethchlorvynol occurs as a colorless to yellow liquid possessing a characteristic pungent odor. It darkens on exposure to light and to air.

Solubility—Ethchlorvynol is immiscible with water. It is miscible with most organic solvents.

Identification—

A: Dissolve 1 g. of Ethchlorvynol in 20 ml. of methanol. To 1 ml. of the solution add about 4 drops of ammonia T.S., mix, and then add silver nitrate T.S., a few drops at a time: a yellowish white precipitate forms which at first redissolves, but becomes insoluble when an excess of silver nitrate has been added.

B: To 10 ml. of the solution prepared in *Identification test A* add 5 ml. of freshly prepared *m*-phenylenediamine hydrochloride-oxalic acid T.S. (prepare the test solution by dissolving 1 g. of *m*-phenylenediamine hydrochloride and 1 g. of oxalic acid in 35 ml. of water, and filtering if necessary): a reddish orange color is produced in about 3 minutes.

Water, page 900—Determine the water content of Ethchlorvynol by the titrimetric method: not more than 0.2 percent is found.

Refractive index, page 858—The refractive index of Ethchlorvynol is not less than 1.476 and not more than 1.480.

Acidity—Dissolve 5 ml. of Ethchlorvynol in 50 ml. of a mixture of equal volumes of water and methanol which has been neutralized to the phenolphthalein end-point with 0.1 *N* sodium hydroxide. Add 1 ml. of phenolphthalein T.S. and titrate with 0.1 *N* sodium hydroxide to an amber end-point: not more than 1.7 ml. of 0.1 *N* sodium hydroxide is required for neutralization.

Assay—Transfer about 110 mg. of Ethchlorvynol, accurately weighed, to a 250-ml. conical flask containing 50 ml. of a solution of silver nitrate (1 in 40) in 70 percent alcohol. Immediately titrate with 0.05 *N* sodium hydroxide, using 8 to 10 drops of methyl red-methylene blue T.S., to a gray end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.05 *N* sodium hydroxide is equivalent to 7.230 mg. of C_7H_9ClO.

Packaging and storage—Preserve Ethchlorvynol in tight, light-resistant glass containers, using polyethylene-lined closures.

CATEGORY—Sedative.

USUAL DOSE—Sedative, **100 mg.** two or three times a day; hypnotic, **500 mg.**

USUAL DOSE RANGE—Sedative, **100** to **200 mg.**; hypnotic, **500 mg.** to **1 g.**

Ethchlorvynol Capsules

Ethchlorvynol Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of C_7H_9ClO.

Identification—Dissolve an amount of the contents of Ethchlorvynol Capsules, equivalent to about 1 g. of ethchlorvynol, in 20 ml. of methanol. The solution responds to the *Identification tests* under *Ethchlorvynol,* page 290.

Weight variation, page 901—Ethchlorvynol Capsules meet the requirements of the weight variation test for capsules, using chloroform as the solvent in the procedure for *Soft capsules*.

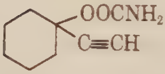
Assay—Weigh accurately 20 Ethchlorvynol Capsules in a tared weighing bottle. Carefully open the capsules, without loss of shell material, and transfer the contents to a 20-ml. beaker. Remove any liquid from the emptied capsules by washing with several small portions of chloroform, and allow the capsules to dry in a jet of dry air until the odor of chloroform is no longer perceptible. Weigh the empty capsules in the original tared weighing bottle. The difference represents the weight of the contents of 20 capsules. Transfer an accurately weighed amount of capsule contents, equivalent to about 110 mg. of ethchlorvynol, to a 250-ml. conical flask containing 50 ml. of a solution of silver nitrate (1 in 40) in 70 percent alcohol. Proceed as directed in the *Assay* under *Ethchlorvynol*, page 290, beginning with "Immediately titrate with 0.05 *N* sodium hydroxide . . ."

Packaging and storage—Preserve Ethchlorvynol Capsules in tight, light-resistant containers.

Capsules available—Ethchlorvynol Capsules usually available contain the following amounts of ethchlorvynol: 100, 200, and 500 mg.

CATEGORY and DOSE—See Ethchlorvynol.

Ethinamate*



1-Ethynylcyclohexanol Carbamate

$C_9H_{13}NO_2$ Mol. wt. 167.21

Ethinamate contains not less than 98.0 percent and not more than 100.5 percent of $C_9H_{13}NO_2$, calculated on the dried basis.

Description—Ethinamate occurs as a white, essentially odorless powder.

Solubility—Ethinamate is slightly soluble in water. It is freely soluble in alcohol, in chloroform, and in ether.

Identification—Dissolve about 100 mg. of Ethinamate in 10 ml. of alcohol, and divide the solution into three equal portions. To one portion add bromine T.S., dropwise: it is instantly decolorized (*presence of unsaturation*). To the second portion add 10 ml. of silver nitrate T.S.: a white precipitate forms. Add 1 ml. of ammonium hydroxide T.S. to the reaction mixture: a yellow color, which slowly deepens, is produced. Add 10 ml. of alcohol to this alkaline mixture: the precipitate dissolves, leaving a yellow to red solution. To the third portion add 10 ml. of water: no precipitate forms.

Melting range, page 814—Ethinamate melts between 95° and 98°.

pH, page 824—The pH of a saturated solution of Ethinamate is between 6.5 and 7.0.

Loss on drying, page 814—Dry Ethinamate in vacuum at 50° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Ethinamate yields not more than 0.2 percent of residue on ignition.

Assay—Transfer about 200 mg. of Ethinamate, accurately weighed, to a 250-ml. glass-stoppered conical flask, and dissolve it in 25 ml. of alcohol. Add 100 ml. of silver nitrate solution (1 in 20), and shake or stir vigorously for 1 to 2 minutes. Using 8 to 10 drops of methyl red-methylene blue T.S., titrate with 0.05 *N* sodium hydroxide to a gray end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.05 *N* sodium hydroxide is equivalent to 8.360 mg. of $C_9H_{13}NO_2$.

Packaging and storage—Preserve Ethinamate in tight containers.

CATEGORY—Sedative.
USUAL DOSE—**500 mg.**
USUAL DOSE RANGE—**500 mg.** to **1 g.**

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* Patented. See notice, page ii.

Ethinamate Tablets

Ethinamate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_2$.

Identification—Transfer to a beaker an amount of powdered Ethinamate Tablets equivalent to about 500 mg. of ethinamate, add 50 ml. of alcohol, mix, and filter. A 10-ml. portion of the filtrate responds to the *Identification tests* under *Ethinamate*, page 292, beginning with "... divide the solution into three equal portions ...."

Disintegration, page 878—The disintegration time limit for Ethinamate Tablets is 30 minutes.

Weight variation, page 901—Ethinamate Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Ethinamate Tablets. Transfer to a flask an accurately weighed portion of the powder, equivalent to about 200 mg. of ethinamate, add 30 ml. of alcohol, and reflux for 20 minutes. Filter while hot, and wash the flask and filter with several small portions of hot alcohol. Evaporate the filtrate to about 25 ml., and proceed as directed in the *Assay* under *Ethinamate*, page 292, beginning with "Add 100 ml. of silver nitrate solution (1 in 20) ...."

Packaging and storage—Preserve Ethinamate Tablets in tight containers.

Tablets available—Ethinamate Tablets usually available contain the following amount of ethinamate: 500 mg.

CATEGORY and DOSE—See Ethinamate.

Ethinyl Estradiol and Dimethisterone Tablets

Ethinyl Estradiol and Dimethisterone Tablets contain not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{20}H_{24}O_2$ (ethinyl estradiol) and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{23}H_{32}O_2 . H_2O$ (dimethisterone).

Identification—Triturate 5 Ethinyl Estradiol and Dimethisterone Tablets with 5 ml. of chloroform, and filter into a separator. Add 20 ml. of *n*-hexane and 20 ml. of sodium hydroxide solution (1 in 10), shake for 1 minute, and allow the layers to separate. Transfer the aqueous phase to a second separator and use in *test A;* retain the chloroform-hexane layer for *test B.*

A: Acidify the aqueous solution in the second separator to litmus paper with diluted sulfuric acid, adding 2 drops in excess, and extract with 10 ml. of chloroform. Transfer the chloroform extract to a beaker containing 1 g. of anhydrous sodium sulfate, mix, and decant the dried chloroform into a test tube. Evaporate the chloroform on a steam bath with the aid of a current of dry air, and add 0.5 ml. of sulfuric acid: the solution appears orange-red by transmitted light and has a yellow-green fluorescence by reflected light; after the addition of 2 ml. of water, the solution is pink or contains a pink precipitate (*presence of ethinyl estradiol*).

B: Transfer the chloroform-hexane solution remaining in the first separator to a 100-ml. beaker containing 1 g. of anhydrous sodium sulfate, mix, decant the dried solution into a second beaker, and evaporate to dryness on a steam bath. Dissolve the residue in 5 ml. of methanol, add 25 ml. of water, and stir until precipitation is completed. Filter the crystals of dimethisterone, wash with water, and dry in vacuum over silica gel. The infrared absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of NF Dimethisterone Reference Standard (*presence of dimethisterone*).

Disintegration, page 878—The disintegration time limit for Ethinyl Estradiol and Dimethisterone Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Ethinyl Estradiol and Dimethisterone Tablets meet the requirements of the content uniformity test for tablets when assayed for dimethisterone only.

Assay for ethinyl estradiol—[NOTE—Use only water as a lubricant for the separators used in this assay.]

Standard preparation—Prepare a solution, in alcohol, containing about 200 mcg. of USP Ethinyl Estradiol Reference Standard per ml., and transfer 1.0 ml. of the solution to a 125-ml. separator containing 25 ml. of water and 5 ml. of diluted sulfuric acid.

Assay preparation—Weigh and finely powder not less than 20 Ethinyl Estradiol and Dimethisterone Tablets. Weigh accurately a portion of the powder, equivalent to about 200 mcg. of ethinyl estradiol, and transfer to a 125-ml. separator containing 25 ml. of water, 1 ml. of alcohol, and 5 ml. of diluted sulfuric acid.

Procedure—Treat the *Standard preparation* and *Assay preparation,* in the two separators, identically, as follows: Extract the solution with four 20-ml. portions of chloroform. Evaporate the combined chloroform extracts to about 5 ml., add about 25 ml. of solvent hexane, and transfer to a 125-ml. separator with the aid of several small portions of solvent hexane. Add 10 ml. of sodium hydroxide solution (1 in 10), shake vigorously for 2 minutes, and allow to separate completely. Transfer the water layer, avoiding withdrawal of any insoluble matter at the interface, to a second 125-ml. separator containing 5 ml. of carbon tetrachloride. Repeat the extraction with two additional 10-ml. portions of the sodium hydroxide solution. Discard the solvent hexane. Shake the alkaline solution vigorously with the carbon tetrachloride, transfer the carbon tetrachloride to another separator, wash it with 5 ml. of the sodium hydroxide solution, discard the carbon tetrachloride, and add the alkaline wash to the main sodium hydroxide extract. (Perform the alkali extractions promptly.) Carefully render the combined alkaline extracts distinctly acid with cooled dilute sulfuric acid (1 in 2), cool thoroughly, and shake for 2 minutes with 20 ml. of benzene. Transfer the water layer to another separator, and extract with a second 20-ml. portion of benzene. Discard the water layer. Wash the benzene solutions in the two separators with two 5-ml. portions of sodium carbonate T.S. and two 5-ml. portions of water, shaking gently to avoid emulsification. Transfer the benzene in the first separator to a beaker, add about 1 g. of powdered anhydrous sodium sulfate, and swirl until entirely clear. Decant the benzene into a 50-ml. volumetric flask. Rinse the first separator with the second 20-ml. portion of benzene, clarify the benzene over the sodium sulfate, and add to the flask. Wash the separators and the beaker with two 4-ml. portions of benzene, add the washings to the flask, and add benzene to volume. (A slight turbidity persisting after standing for 5 minutes in the benzene extracts may be ignored if the interface is sharply defined.)

Transfer in duplicate to dry 23 × 150-mm. test tubes 10.0 ml. of each of the benzene solutions, add a few boiling chips to each tube, and evaporate the solvent on a steam bath without the aid of a current of air, until ebullition just stops. Instantly remove the tubes, wipe them dry quickly, and dry the residue in vacuum over phosphorus pentoxide for 1 hour. To each tube and to a blank tube add a glass bead and add from a buret 1.0 ml. of iron-phenol T.S. Immediately cap the tubes, and allow to stand for 30 minutes, shaking vigorously at 5-minute intervals. Place the tubes in a boiling water bath for 35 minutes, shaking each tube for a few seconds after the first 5 minutes. Transfer to an ice bath for 2 minutes, then remove, and add from a buret 4.0 ml. of dilute sulfuric acid (35 volumes of acid added to 65 volumes of water). Allow to stand for 5 minutes, then mix by shaking, first gently, then vigorously. Concomitantly determine the absorbances of the solutions from the *Standard preparation* and from the *Assay preparation*, in 1-cm. cells, at 529 mμ and at 420 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Calculate the quantity, in mcg., of $C_{20}H_{24}O_2$ in the portion of the Tablets taken by the formula $C \times (A_{\Delta U}/A_{\Delta S})$, in which C is the exact concentration, in mcg. per ml., of USP Ethinyl Estradiol Reference Standard in the *Standard preparation*, $A_{\Delta U}$ is the difference obtained by subtracting one-half of the absorbance (A_{420}) observed at 420 mμ from that (A_{529}) observed at 529 mμ for the solution from the *Assay preparation*, and $A_{\Delta S}$ is the difference obtained similarly for the solution from the *Standard preparation*.

Assay for dimethisterone—

Isoniazid reagent—Dissolve 500 mg. of isonicotinic acid hydrazide in 100 ml. of methanol, add 0.5 ml. of hydrochloric acid, and mix.

Standard preparation—Transfer about 50 mg. of NF Dimethisterone Reference Standard, accurately weighed, to a 50-ml. volumetric flask, add chloroform to volume, and mix. Transfer 5.0 ml. of this solution to a second 50-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparation—Weigh and finely powder not less than 20 Ethinyl Estradiol and Dimethisterone Tablets. Weigh accurately a portion of the powder, equivalent to about 25 mg. of dimethisterone, and transfer it to a 60-ml. separator with the aid of about 10 ml. of water. Add 25 ml. of chloroform, and shake for about 5 minutes. Filter the chloroform layer through a chloroform-washed cotton pledget into a 100-ml. volumetric flask. Repeat the extraction with two 25-ml. portions of chloroform, and wash the cotton with chloroform, receiving the washings in the same flask. Dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this solution to a 25-ml. volumetric flask, dilute to volume with chloroform, and mix.

Procedure—Transfer 2.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of chloroform to serve as the blank, to separate 50-ml. glass-stoppered conical flasks. To each flask add 10.0 ml. of *Isoniazid reagent*, mix, and allow to stand for 30 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 380 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{23}H_{32}O_2.H_2O$ in the portion of the Tablets taken by the formula $0.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

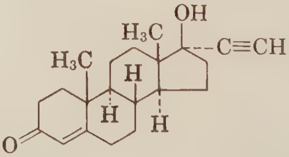
Packaging and storage—Preserve Ethinyl Estradiol and Dimethisterone Tablets in well-closed containers.

Tablets available—Ethinyl Estradiol and Dimethisterone Tablets usually available contain the following amount of ethinyl estradiol: 100 mcg.; and of dimethisterone: 25 mg.

CATEGORY—Estrogen-progestin (ovulation control).

USUAL DOSE—Ethinyl estradiol, **100 mcg.** daily for 20 days of each menstrual cycle; dimethisterone, **25 mg.** daily for 5 days of each cycle.

Ethisterone



17-Hydroxy-17α-pregn-4-en-20-yn-3-one

$C_{21}H_{28}O_2$ Mol. wt. 312.46

Ethisterone contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{28}O_2$, calculated on the dried basis.

Description—Ethisterone occurs as white or slightly yellow crystals or as a crystalline powder. It is odorless and is stable in air. It is affected by light.

Solubility—Ethisterone is practically insoluble in water. It is slightly soluble in alcohol, in chloroform, in ether, and in vegetable oils.

Identification—Reflux about 25 mg. of Ethisterone for 5 hours with 3.5 ml. of a solution prepared by dissolving 50 mg. of hydroxylamine hydrochloride and 50 mg. of anhydrous sodium acetate in 25 ml. of methanol. Add to the solution 15 ml. of water, filter, and wash the precipitate with a small volume of water: the precipitated oxime, when recrystallized from 70 percent methanol and dried at 105° for 1 hour, melts between 225° and 232°, page 814.

Melting range, *Class Ia,* page 815—Ethisterone melts between 267° and 277°, with some decomposition.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Ethisterone, previously dried over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Ethisterone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Ethisterone in methanol exhibits maxima and minima at the same wavelengths as that of NF Ethisterone Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Ethisterone, previously dried in vacuum over silica gel for 4 hours, determined in a solution in pyridine containing 100 mg. of Ethisterone in each 10 ml., is between +29° and +33°.

Loss on drying, page 814—Dry Ethisterone in vacuum over silica gel for 4 hours: it loses not more than 0.5 percent of its weight.

Foreign steroids and other impurities—*Standard preparation*—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Ethisterone Reference Standard, previously dried in vacuum over silica gel for 4 hours, and dioxane as the solvent.

Test preparation—Weigh accurately about 80 mg. of Ethisterone, previously dried in vacuum over silica gel for 4 hours, dissolve it in a sufficient quantity of dioxane to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of chloroform and ethyl acetate (2:1). Use 25.0 ml. of dioxane, rather than dehydrated alcohol, to elute the steroid from the silica gel. Determine the absorbance at the maximum at about 235 mμ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Ethisterone taken: not more than 3 percent is found.

Assay—Transfer about 25 mg. of Ethisterone, accurately weighed, to a 250-ml. volumetric flask, add 50 ml. of methanol, dissolve by heating on a steam bath, and cool. Dilute to volume with methanol, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Ethisterone Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{21}H_{28}O_2$ in the Ethisterone taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Ethisterone in well-closed, light-resistant containers.

CATEGORY—Progestin.

USUAL DOSE—**25 mg.** up to four times a day.

Ethisterone Tablets

Ethisterone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{28}O_2$.

Identification—The ethisterone obtained in the *Assay* melts between 266° and 277°, with some decomposition, *Class Ia,* page 815, and responds to the *Identification test* under *Ethisterone,* page 294.

Disintegration, page 878—The disintegration time limit for Ethisterone Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Ethisterone Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask, add 50 ml. of methanol, mix, and shake mechanically for 30 minutes. Dilute to volume with methanol, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol to provide a solution containing approximately 5 mcg. of ethisterone per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Ethisterone Reference Standard, in the same medium at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{21}H_{28}O_2$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of ethisterone, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of ethisterone in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Other requirements—The ethisterone obtained in the *Assay* meets the requirements of the test for *Specific rotation*, under *Ethisterone*, page 294.

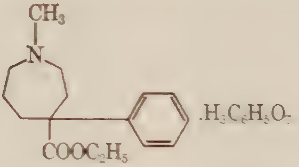
Assay—Weigh and finely powder not less than 20 Ethisterone Tablets. Weigh accurately a portion of the powder, equivalent to about 100 mg. of ethisterone, into the thimble of a micro continuous-extraction apparatus, extract with solvent hexane for 4 hours, and discard the extract. Remove the thimble from the extractor, and allow the solvent hexane to evaporate. Return the thimble to the extractor, replace the solvent flask with a tared flask, and extract the ethisterone with chloroform for 4 hours. Evaporate the extract almost to dryness, remove the last traces of chloroform at room temperature with the aid of a current of air, dry at 105° for 2 hours, and cool: the weight of the residue is the amount of $C_{21}H_{28}O_2$ in the portion of the Tablets taken.

Packaging and storage—Preserve Ethisterone Tablets in well-closed containers.

Tablets available—Ethisterone Tablets usually available contain the following amounts of ethisterone: 5, 10, and 25 mg.

Category and Dose—See Ethisterone.

Ethoheptazine Citrate*



Ethyl Hexahydro-1-methyl-4-phenyl-1*H*-azepine-4-carboxylate Citrate (1:1)

$C_{16}H_{23}NO_2 . C_6H_8O_7$ Mol. wt. 453.49

Ethoheptazine Citrate, dried at 60° in vacuum for 3 hours, contains not less than 97.0 percent and not more than 102.0 percent of $C_{16}H_{23}NO_2 . C_6H_8O_7$.

Description—Ethoheptazine Citrate occurs as a white to nearly white, practically odorless powder.

Solubility—Ethoheptazine Citrate is sparingly soluble in water, slightly soluble in alcohol, and insoluble in ether.

Identification—Dissolve about 100 mg. of Ethoheptazine Citrate in 10 ml. of alcohol, add, with stirring, 5 ml. of an alcoholic solution of picric acid (1 in 15), and allow to stand overnight. Filter the precipitate, wash with a few small portions of water, and dry at 105° for 2 hours: the picrate so obtained melts between 163° and 170°, page 814. *Caution: Picrates may be explosive.*

Melting range, page 814—Ethoheptazine Citrate melts within a range of 3° between 135° and 145°.

pH, page 824—The pH of a solution of Ethoheptazine Citrate (1 in 100) is between 3.5 and 4.5.

Loss on drying, page 814—Dry Ethoheptazine Citrate in vacuum at 60° for 3 hours: it loses not more than 3 percent of its weight.

Residue on ignition, page 858—Ethoheptazine Citrate yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 900 mg. of

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* Patented. See notice, page ii.

Ethoheptazine Citrate, previously dried in vacuum at 60° for 3 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 45.35 mg. of $C_{16}H_{23}NO_2 . C_6H_8O_7$.

Packaging and storage—Preserve Ethoheptazine Citrate in tight containers.

Category—Analgesic.

Usual dose—**75 mg.** three or four times a day.

Usual dose range—**75** to **150 mg.**

Ethoheptazine Citrate Tablets

Ethoheptazine Citrate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{23}NO_2 . C_6H_8O_7$.

Identification—Macerate a portion of finely powdered Ethoheptazine Citrate Tablets, equivalent to about 200 mg. of ethoheptazine citrate, with 10 ml. of alcohol, and transfer to a 50-ml. beaker. Add 20 ml. of alcohol, warm to dissolve as completely as possible, cool the solution, and filter through paper into a 50-ml. glass-stoppered conical flask. This solution responds to the *Identification test* under *Ethoheptazine Citrate*, page 298.

Disintegration, page 878—The disintegration time limit for Ethoheptazine Citrate Tablets is 15 minutes.

Weight variation, page 901—Ethoheptazine Citrate tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Ethoheptazine Citrate Tablets. Transfer an accurately weighed portion of the powder, equivalent to 150 mg. of ethoheptazine citrate, to a separator, add 20 ml. of alkaline sodium chloride T.S., stopper, and shake vigorously for about 5 minutes. Extract with five 30-ml. portions of carbon tetrachloride, filtering the extracts through a pledget of cotton overlaid with anhydrous sodium sulfate, both previously wetted with carbon tetrachloride, into a 250-ml. wide-mouth conical flask. Add 20 ml. of glacial acetic acid and 2 drops of crystal violet T.S., and titrate with 0.025 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.025 *N* perchloric acid is equivalent to 11.34 mg. of $C_{16}H_{23}NO_2 . C_6H_8O_7$.

Packaging and storage—Preserve Ethoheptazine Citrate Tablets in tight containers.

Tablets available—Ethoheptazine Citrate Tablets usually available contain the following amount of ethoheptazine citrate: 75 mg.

Category and Dose—See Ethoheptazine Citrate.

Ethyl Acetate

$CH_3COOC_2H_5$

$C_4H_8O_2$ Mol. wt. 88.11

Ethyl Acetate contains not less than 99.0 percent and not more than 100.5 percent of $C_4H_8O_2$.

Description—Ethyl Acetate is a transparent, colorless liquid, with a fragrant, refreshing, slightly acetous odor, and a peculiar, acetous, burning taste.

Solubility—Ethyl Acetate is soluble in water. It is miscible with alcohol, ether, fixed oils, and volatile oils.

Identification—Ethyl Acetate is readily volatilized even at low temperatures and is flammable; when burned, a yellow flame and an acetous odor are produced.

Specific gravity, page 866—The specific gravity of Ethyl Acetate is not less than 0.894 and not more than 0.898.

Distilling range, page 782—Ethyl Acetate distils between 76° and 77.5°.

Acidity—A solution of 2 ml. of Ethyl Acetate in 10 ml. of neutralized alcohol requires not more than 0.1 ml. of 0.1 *N* sodium hydroxide for neutralization, using 2 drops of phenolphthalein T.S. as the indicator.

Nonvolatile residue—Evaporate Ethyl Acetate in a tared porcelain dish on a steam bath and dry at 105° for 1 hour: not more than 0.02 percent of residue remains.

Readily carbonizable substances—Pour 2 ml. of Ethyl Acetate carefully upon 10 ml. of sulfuric acid T.S. so as to form separate layers: no dark zone is developed within 15 minutes.

Butyl or amyl derivatives—Allow 10 ml. of Ethyl Acetate to evaporate spontaneously from clean, odorless blotting-paper: the final odor does not resemble that of pineapple or banana.

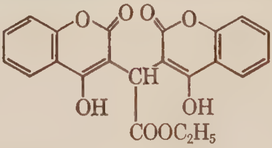
Methyl compounds—Place 20 ml. of Ethyl Acetate in a 500-ml. separator, add a solution of 20 g. of sodium hydroxide in 50 ml. of water, stopper the separator, and wrap it securely in a towel for protection against the heat of the reaction. Shake the mixture vigorously for about 5 minutes, cautiously opening the stopcock from time to time to permit the escape of air. Continue shaking vigorously until a homogeneous liquid results, then distil and collect about 25 ml. of the distillate. To 50 μl. of the distillate add 1 drop of dilute phosphoric acid (1 in 20), and 1 drop of potassium permanganate solution (1 in 20). Mix, allow to stand 1 minute, and add sodium bisulfite solution (1 in 20), dropwise, until the permanganate color is discharged. If a brown color remains, add 1 drop of the dilute phosphoric acid. To the colorless solution add 5 ml. of freshly prepared chromotropic acid T.S. and heat on a steam bath for 10 minutes at 60°: no violet color appears.

Assay—Transfer about 1.5 g. of Ethyl Acetate, accurately weighed in a tared, stoppered weighing bottle, to a suitable flask, add 50.0 ml. of 0.5 *N* sodium hydroxide, and heat on a steam bath under a reflux condenser for 1 hour. Allow it to cool, add phenolphthalein T.S., and titrate the excess sodium hydroxide with 0.5 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.5 *N* sodium hydroxide is equivalent to 44.05 mg. of $C_4H_8O_2$.

Packaging and storage—Preserve Ethyl Acetate in tight containers and avoid excessive heat.

CATEGORY—Flavor.

Ethyl Biscoumacetate



Ethyl Bis(4-hydroxy-2-oxo-2*H*-1-benzopyran-3-yl)acetate

$C_{22}H_{16}O_8$ Mol. wt. 408.37

Ethyl Biscoumacetate, dried at 105° for 2 hours, contains not less than 97.0 percent and not more than 101.0 percent of $C_{22}H_{16}O_8$.

Description—Ethyl Biscoumacetate occurs as a white to yellowish white, crystalline powder.

Solubility—Ethyl Biscoumacetate is soluble in acetone and in benzene. It is slightly soluble in alcohol and in ether. It is insoluble in water.

Identification—

A: Dissolve 25 mg. of Ethyl Biscoumacetate in 5 ml. of alcohol and add a few drops of ferric chloride T.S.: a reddish brown color is produced.

B: Dissolve 500 mg. of Ethyl Biscoumacetate in 3 ml. of 2 *N* sodium hydroxide and allow the solution to stand for several hours, then add about 0.5 ml. of 0.1 *N* iodine: the odor of iodoform is perceptible.

Melting range, *Class Ia*, page 815—Ethyl Biscoumacetate exists in two tautomeric forms, melting between 153° and 158°, and between 177° and 182°.

Loss on drying, page 814—Dry Ethyl Biscoumacetate at 105° for 2 hours: it loses not more than 0.3 percent of its weight.

Residue on ignition, page 858—Ethyl Biscoumacetate yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Ethyl Biscoumacetate is 10 parts per million.

Assay—Dissolve about 600 mg. of Ethyl Biscoumacetate, previously dried at 105° for 2 hours and accurately weighed, in 25 ml. of acetone. Heat gently to dissolve, cool the solution, add 5 drops of methyl red T.S., and titrate with 0.1 *N* sodium hydroxide to the first yellow color. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 40.84 mg. of $C_{22}H_{16}O_8$.

Packaging and storage—Preserve Ethyl Biscoumacetate in tight containers.

CATEGORY—Anticoagulant.

USUAL DOSE—Initial, **1.2** to **1.8 g.,** then **300** to **900 mg.** daily in accordance with prothrombin time determinations.

Ethyl Biscoumacetate Tablets

Ethyl Biscoumacetate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{22}H_{16}O_8$.

Identification—Macerate a portion of powdered Ethyl Biscoumacetate Tablets, equivalent to 300 mg. of ethyl biscoumacetate, with 10 ml. of warm acetone. Filter into a test tube, concentrate the filtrate to about 2.5 ml. on a steam bath, and allow to cool. Collect the crystalline precipitate by filtration, and dry the crystals at 100° for 30 minutes. The ethyl biscoumacetate so obtained melts between 151° and 158°, page 814, and responds to the *Identification tests* under *Ethyl Biscoumacetate*, page 298.

Disintegration, page 878—The disintegration time limit for Ethyl Biscoumacetate Tablets, using simulated gastric fluid T.S., is 5 minutes.

Weight variation, page 901—Ethyl Biscoumacetate Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Ethyl Biscoumacetate Tablets. Weigh accurately a portion of powder equivalent to about 750 mg. of ethyl biscoumacetate, and transfer to a 250-ml. beaker. Add 100 ml. of benzene, warm on a steam bath, stirring to dissolve the ethyl biscoumacetate, then filter through a fine sintered-glass funnel, receiving the filtrate in a second 250-ml. beaker. Wash the beaker and funnel with small portions of warm benzene, adding the washings to the filtrate. Evaporate the filtrate to dryness on a steam bath with the aid of a gentle stream of air. Add 30 ml. of acetone to the dried residue, and heat to dissolve. Cool, add 10 to 15 drops of methyl red T.S., and titrate with 0.1 *N* sodium hydroxide. Perform a blank titration on 30 ml. of acetone, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 40.84 mg. of $C_{22}H_{16}O_8$.

Packaging and storage—Preserve Ethyl Biscoumacetate Tablets in tight containers.

Tablets available—Ethyl Biscoumacetate Tablets usually available contain the following amounts of ethyl biscoumacetate: 150 and 300 mg.

CATEGORY and DOSE—See Ethyl Biscoumacetate.

Ethyl Chloride

CH_3CH_2Cl

Chloroethane

C_2H_5Cl Mol. wt. 64.52

Ethyl Chloride contains not less than 99.5 percent and not more than 100.5 percent of C_2H_5Cl.

Caution—Ethyl Chloride is highly flammable. Do not use where it may be ignited.

Description—Ethyl Chloride occurs as a colorless, mobile, very volatile liquid at low temperatures or under pressure, having a characteristic, ethereal odor. Ethyl Chloride boils between 12° and 13°, and its specific gravity is about 0.921 at 0°. When liberated at room temperature from its sealed container, it vaporizes at once. It burns with a smoky, greenish flame, producing hydrogen chloride.

Solubility—Ethyl Chloride is slightly soluble in water and is freely soluble in alcohol and in ether.

Reaction—Shake 10 ml. of Ethyl Chloride with 10 ml. of water, both having been previously cooled to 0°, and allow the supernatant layer of ethyl chloride to volatilize spontaneously: the remaining liquid is neutral to litmus. Retain the liquid for the test for *Alcohol.*

Nonvolatile residue, and odor—Allow 5 ml. of Ethyl Chloride to evaporate spontaneously from a tared, shallow dish: no foreign odor is perceptible while the last portions evaporate, and the weight of the residue is negligible.

Chloride—Add a few drops of silver nitrate T.S. to 10 ml. of alcohol, cool to 0°, and add to the clear liquid about 0.5 ml. of Ethyl Chloride cooled to the same temperature: no turbidity is produced immediately.

Alcohol—To the liquid obtained in the test for *Reaction* add a few drops of potassium dichromate T.S. and 2 ml. of diluted sulfuric acid, and boil the mixture: no odor of acetaldehyde is perceptible, and no greenish or purplish color is produced.

Assay—Introduce about 1.5 ml. of cold Ethyl Chloride into a tared glass-stoppered bottle containing 25.0 ml. of 1 *N* alcoholic potassium hydroxide, rapidly replace the stopper, and weigh accurately. Tie down the stopper, heat in a boiling water bath for 30 minutes, and cool. Remove the stopper, add 3 drops of phenolphthalein T.S., and titrate the excess alkali with 1 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 1 *N* alcoholic potassium hydroxide is equivalent to 64.52 mg. of C_2H_5Cl.

Packaging and storage—Preserve Ethyl Chloride in tight containers, preferably hermetically sealed, and remote from fire.

CATEGORY—Local anesthetic.

FOR EXTERNAL USE—Topically, as spray on intact skin.

Ethylcellulose

Ethylcellulose is an ethyl ether of cellulose containing not less than 44.0 percent and not more than 51.0 percent of ethoxy ($—OC_2H_5$) groups, calculated on the dried basis. The viscosity of a 5 percent (w/w) solution of medium-type Ethylcellulose, containing less than 46.5 percent of ethoxy groups, in a mixture of 60 parts of toluene and 40 parts of alcohol, by weight, is not less than 90.0 percent and not more than 110.0 percent of that stated on the label in centipoises. The viscosity of a 5 percent (w/w) solution of standard-type Ethylcellulose, containing 46.5 percent or more of ethoxy groups, in a mixture of 80 parts of toluene and 20 parts of alcohol, by weight, is not less than 90.0 percent and not more than 110.0 percent of that stated on the label in centipoises, with the exception that the 7-centipoise viscosity grade may vary between 6.0 and 8.0 centipoises and the 4-centipoise viscosity grade may vary between 3.0 and 5.5 centipoises.

Description—Ethylcellulose occurs as a free flowing, white to light tan powder. It forms films that have a refractive index of about 1.47. Its aqueous suspensions are neutral to litmus.

Solubility—Medium type Ethylcellulose is freely soluble in tetrahydrofuran, in methyl acetate, in chloroform, and in mixtures of aromatic hydrocarbons with alcohol. Standard-grade Ethylcellulose is freely soluble in alcohol, in methanol, in toluene, in chloroform, and in ethyl acetate. Both types are insoluble in water, in glycerin, and in propylene glycol

Identification—

A: Dissolve 5 g. of Ethylcellulose in 95 g. of a mixture of 80 parts of toluene and 20 parts of alcohol, by weight: a clear, stable, slightly yellow solution results.

B: Pour a few ml. of the solution of Ethylcellulose prepared in *Identification test A* on a glass plate and allow the solvent to evaporate: a thin, tough, continuous, clear film remains. The film is flammable.

Loss on drying, page 814—Dry Ethylcellulose at 105° for 2 hours: it loses not more than 3 percent of its weight.

Residue on ignition, page 858—Ethylcellulose yields not more than 0.4 percent of residue on ignition.

Viscosity—

Solvent systems—For medium type Ethylcellulose prepare a solvent system consisting of 60 parts of toluene and 40 parts of alcohol, by weight. For standard type Ethylcellulose prepare a solvent system consisting of 80 parts of toluene and 20 parts of alcohol, by weight.

Procedure—Transfer an accurately weighed portion of Ethylcellulose, equivalent to 5.0 g. on the dried basis, into a bottle containing 95 ± 0.05 g. of the appropriate solvent system. Shake or tumble the bottle until the sample is completely dissolved. Adjust the temperature of the solution to 25° ± 0.1° and determine the viscosity as described under *Procedure for Cellulose Derivatives,* page 889, but make all determinations at 25°/25° instead of 20°/20° as directed therein.

Assay—Place about 50 mg. of Ethylcellulose in an empty tared gelatin capsule. Weigh the Ethylcellulose accurately and transfer the capsule and contents to the boiling flask of an alkoxyl apparatus. Proceed as directed under *Methoxy Determination,* page 817. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 0.7510 mg. of ($—OC_2H_5$).

Packaging and storage—Preserve Ethylcellulose in well-closed containers.

Labeling—Label Ethylcellulose to indicate the type (low or high ethoxy content, i.e., medium or standard type) and viscosity of its solution (under the conditions specified above).

CATEGORY—Tablet binder.

Ethylene

$CH_2{=}CH_2$

C_2H_4 Mol. wt. 28.05

Ethylene contains not less than 99.0 percent by volume of C_2H_4.

Caution: Ethylene is highly flammable. Do not use where it may be ignited.

Note: Maintain cylinders of Ethylene at 25° ± 2° for at least 6 hours prior to withdrawing samples for the tests and assay, and correct the results to 25° and 760 mm. of mercury.

Description—Ethylene is a colorless gas, somewhat lighter than air, and has a slightly sweet odor and taste. One liter of Ethylene at a pressure of 760 mm. of mercury and at 0° weighs 1.260 g.

Solubility—One volume of Ethylene dissolves in about 4 volumes of water at 0° and in about 9 volumes of water at 25°. One volume of it dissolves in about 0.5 volume of alcohol at 25° and in about 0.05 volume of ether at 15.5°.

Identification—

A: Ethylene is slowly soluble in sulfuric acid but is rapidly absorbed by fuming sulfuric acid and by concentrated solutions of potassium permanganate.

B: Bubble Ethylene through bromine T.S.: the reagent is decolorized.

Acidity or alkalinity—Mix 0.3 ml. of methyl red T.S. and 0.3 ml. of bromothymol blue T.S. with 400 ml. of boiling water, and boil the solution for 5 minutes. Pour 100 ml. of the boiling solution into each of three similar, clear-glass color-comparison tubes. Add 0.2 ml. of 0.01 *N* hydrochloric acid to one tube (A), and 0.4 ml. of 0.01 *N* hydrochloric acid to the second tube (B). Stopper each of the tubes, and cool them to room temperature. Pass 2000 ml. of Ethylene through the solution in tube A at a rate requiring about 30 minutes for the passage of the gas. The color of the solution in tube A is no deeper orange-red than that of the solution in tube B and no deeper yellow-green than that of the untreated solution in the third tube.

Carbon dioxide—Pass 1000 ml. of Ethylene through 50 ml. of clear barium hydroxide T.S., contained in a vessel of such size and shape that the depth of the solution is from 12 to 14 cm., employing a delivery tube with an orifice approximately 1 mm. in diameter and extending to within 2 mm. of the bottom of the vessel, and regulating the flow of the Ethylene so as to require approximately 15 minutes for the delivery of 1000 ml. Any turbidity produced does not exceed that produced when 1 ml. of a solution of 100 mg. of sodium bicarbonate in 100 ml. of carbon dioxide-free water is added to 50 ml. of clear barium hydroxide T.S. (about 0.04 percent).

Acetylene, aldehyde, hydrogen sulfide, phosphine—Under the conditions prescribed in the test for *Carbon dioxide*, pass 1000 ml. of Ethylene through 25 ml. of silver ammonium nitrate T.S.: no turbidity or darkening is produced.

Carbon monoxide—Collect, in separate, suitable flasks, 1000 ml. of Ethylene and 1000 ml. of air obtained at a place removed from sources of carbon monoxide. Immediately add to each flask 2.5 ml. of a blood solution prepared by adding 10 ml. of water to 0.5 ml. of blood, and mixing thoroughly. Stopper the flasks and shake frequently during 15 minutes. To each flask add 40 mg. of a mixture of equal parts by weight of pyrogallol and tannic acid. Shake thoroughly, and allow the flasks to stand in the dark for 15 minutes. Pour the contents of each flask into a test tube for observation. The solution from the Ethylene being tested shows no pink coloration and matches the gray color produced in the solution from the air.

Assay—Place a sufficient quantity of clean mercury in a 100-ml. gas buret or nitrometer provided with a two-way stopcock and a two-way outlet and properly connected with a balancing tube. Connect one of the outlet tubes with a gas pipet of suitable capacity containing 125 ml. of bromine T.S. By proper manipulation of the balancing tube, draw the bromine T.S. (excluding bubbles of air) through the capillary of the pipet, the outlet tube, and the bore of the stopcock of the buret, and at once close the stopcock. Now by reversing the movement of the balancing tube, completely fill the buret, the other bore of the stopcock, and the other outlet tube with mercury. Draw into the buret about 105 ml. of Ethylene by again lowering the balancing tube. Disconnect the container of gas, and, with the stopcock open, adjust the volume of Ethylene to 100.0 ml., having the level of the mercury exactly the same in the buret and balancing tube, and close the stopcock. Raise the balancing tube to increase the pressure in the buret, and open the other bore of the stopcock, forcing all of the Ethylene into the gas pipet. Close the stopcock, and rock the gas pipet gently for 5 minutes. Open the stopcock, lower the balancing bulb to draw the gas completely back to the buret, then raise the balancing tube, and force the gas once more into the pipet. Gently rock the pipet until there is no further apparent diminution of the volume of the gas. Draw the residual gas completely into the buret, close the stopcock, remove the bromine pipet, and replace it with one containing a saturated solution of potassium hydroxide. Force the residual gas into the pipet, rock it gently for 5 minutes, return the gas to the buret, close the bore of the stopcock, and equalize the height of mercury in the two tubes of the buret: not more than 1 ml. of gas remains.

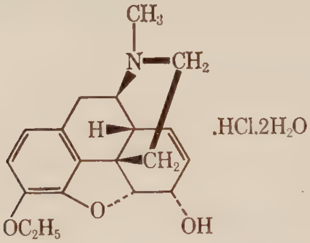
Packaging and storage—Preserve Ethylene in cylinders, remote from fire.

Labeling—Label Ethylene with the statement "*Caution: Ethylene is flammable, and a mixture of it with oxygen or air will explode when brought in contact with a flame or other cause of ignition.*"

CATEGORY—General anesthetic.

APPLICATION—By inhalation as required.

Ethylmorphine Hydrochloride



7,8-Didehydro-4,5α-epoxy-3-ethoxy-17-methylmorphinan-6α-ol Hydrochloride

$C_{19}H_{23}NO_3 . HCl . 2H_2O$ Mol. wt. 385.89

Ethylmorphine Hydrochloride contains not less than 99.0 percent and not more than 100.5 percent of $C_{19}H_{23}NO_3 . HCl$, calculated on the anhydrous basis.

Description—Ethylmorphine Hydrochloride occurs as a white or faintly yellow, odorless, microcrystalline powder. It melts with decomposition at about 123°.

Solubility—Ethylmorphine Hydrochloride is soluble in water and in alcohol. It is slightly soluble in ether and in chloroform.

Identification—

A: To a solution of about 10 mg. of Ethylmorphine Hydrochloride in 10 ml. of sulfuric acid add a drop of ferric chloride T.S., and warm it on a steam bath: the mixture at first becomes green, then deep violet-blue, and after the addition of a drop of nitric acid, deep red.

B: A solution of Ethylmorphine Hydrochloride responds to the tests for *Chloride*, page 808.

Specific rotation, page 822—The specific rotation of Ethylmorphine Hydrochloride, calculated on the anhydrous basis, determined in a solution containing 200 mg. of Ethylmorphine Hydrochloride in each 10 ml., is between −102° and −105°.

Distinction from codeine hydrochloride—To 5 ml. of a solution of Ethylmorphine Hydrochloride (1 in 25) add 1 ml. of ammonia T.S.: a white turbidity is produced immediately.

Acidity—Dissolve 500 mg. of Ethylmorphine Hydrochloride in 15 ml. of water, add 1 drop of methyl red T.S., and titrate with 0.02 *N* sodium hydroxide: not more than 0.3 ml. is required to produce a yellow color.

Water, page 900—Determine the water content of Ethylmorphine Hydrochloride by the titrimetric method: not less than 8 percent and not more than 10 percent is found.

Residue on ignition, page 858—The residue on ignition from 200 mg. of Ethylmorphine Hydrochloride is negligible.

Ammonium compounds—Heat 5 ml. of a solution of Ethylmorphine Hydrochloride (1 in 20) with 5 ml. of sodium hydroxide T.S. in a test tube in a water bath: moistened red litmus paper held in the escaping vapors does not turn blue immediately.

Morphine—Dissolve about 50 mg. of potassium ferricyanide in 10 ml. of water, and add 1 ml. of diluted ferric chloride solution (1 volume of ferric chloride T.S. to 9 volumes of water) and 1 ml. of a solution of Ethylmorphine Hydrochloride (1 in 100): no green or blue color is produced immediately.

Assay—Dissolve about 700 mg. of Ethylmorphine Hydrochloride, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S. and 10 ml.

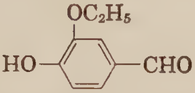
of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 34.99 mg. of $C_{19}H_{23}NO_3 . HCl$.

Packaging and storage—Preserve Ethylmorphine Hydrochloride in tight, light-resistant containers.

CATEGORY—Chemotic.

APPLICATION—Topically as a 1 to 5 percent solution in the eye.

Ethyl Vanillin



3-Ethoxy-4-hydroxybenzaldehyde

$C_9H_{10}O_3$ Mol. wt. 166.18

Ethyl Vanillin, dried over phosphorus pentoxide for 4 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_9H_{10}O_3$.

Description—Ethyl Vanillin occurs as fine white or slightly yellowish crystals. Its taste and odor are similar to the taste and odor of vanillin. It is affected by light. Its solutions are acid to litmus.

Solubility—Ethyl Vanillin is sparingly soluble in water at 50°. It is freely soluble in alcohol, in chloroform, in ether, and in solutions of alkali hydroxides.

Identification—

A: Warm about 100 mg. of Ethyl Vanillin with 1 ml. of 25 percent hydrochloric acid until complete solution is effected. Cool, add about 1 ml. of hydrogen peroxide T.S., and allow the mixture to stand, with frequent shaking, until precipitation is complete (10 to 20 minutes). Add an equal volume of benzene and shake thoroughly: the benzene layer is violet in color (*distinction from vanillin*).

B: Ethyl Vanillin is extracted completely from its solution in ether by shaking with a saturated solution of sodium bisulfite, from which it is precipitated by acids.

C: To a cold solution of Ethyl Vanillin add lead subacetate T.S.: a white precipitate is produced which is sparingly soluble in hot water, but soluble in acetic acid.

Melting range, page 814—Ethyl Vanillin melts between 76° and 78°.

Loss on drying, page 814—Dry Ethyl Vanillin over phosphorus pentoxide for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Ethyl Vanillin yields not more than 0.05 percent of residue on ignition.

Assay—Dissolve about 300 mg. of Ethyl Vanillin, previously dried for 4 hours over phosphorus pentoxide and accurately weighed, in 50 ml. of dimethylformamide contained in a 125-ml. conical flask. Add 3 drops of thymol blue T.S., and titrate with 0.1 *N* sodium methoxide, using a magnetic stirrer and taking precautions against the absorption of atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium methoxide is equivalent to 16.62 mg. of $C_9H_{10}O_3$.

Packaging and storage—Preserve Ethyl Vanillin in tight, light-resistant containers.

CATEGORY—Flavor.

Eucalyptus Oil

Eucalyptus Oil is the volatile oil distilled with steam from the fresh leaf of *Eucalyptus globulus* Labillardière or of some other species of *Eucalyptus* L'Heritier (Fam. *Myrtaceæ*). Eucalyptus Oil contains not less than 70.0 percent of $C_{10}H_{18}O$ (eucalyptol).

Description—Eucalyptus Oil is a colorless or pale yellow liquid, having a characteristic, aromatic, somewhat camphoraceous odor, and a pungent, spicy, cooling taste.

Solubility test—One volume of Eucalyptus Oil is soluble in 5 volumes of 70 percent alcohol.

Specific gravity, page 866—The specific gravity of Eucalyptus Oil is not less than 0.905 and not more than 0.925.

Congealing temperature, page 794—

Eucalyptus Oil congeals at a temperature not lower than −15.4°, indicating not less than 70.0 percent of $C_{10}H_{18}O$ (eucalyptol).

Refractive index, page 858—The refractive index of Eucalyptus Oil is not less than 1.458 and not more than 1.470 at 20°.

Heavy metals, page 806—Eucalyptus Oil meets the requirements of the test for heavy metals in volatile oils.

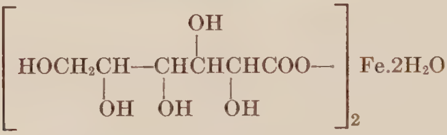
Phellandrene—Mix 2.5 ml. of Eucalyptus Oil with 5 ml. of solvent hexane, add 5 ml. of a solution of sodium nitrite made by dissolving 5 g. of sodium nitrite in 8 ml. of water, then gradually add 5 ml. of glacial acetic acid: no crystals form in the mixture within 10 minutes.

Packaging and storage—Preserve Eucalyptus Oil in tight containers.

Category—Flavor.

Eugenol-Zinc Cement, page 766

Ferrous Gluconate



$$\left[\mathrm{HOCH_2}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{{-}}\underset{\mathrm{OH}}{\mathrm{CH}}\overset{\mathrm{OH}}{\mathrm{C}}\mathrm{H}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{COO{-}}\right]_2\mathrm{Fe.2H_2O}$$

Iron (2+) Gluconate

$C_{12}H_{22}FeO_{14}.2H_2O$ Mol. wt. 482.18

Ferrous Gluconate, dried at 105° for 4 hours, contains not less than 95.0 percent and not more than 100.5 percent of $C_{12}H_{22}FeO_{14}$.

Description—Ferrous Gluconate occurs as a yellowish gray or pale greenish yellow, fine powder or granules having a slight odor resembling that of burned sugar. Its 1 in 20 solution is acid to litmus.

Solubility—Ferrous Gluconate is soluble in water with slight heating. It is practically insoluble in alcohol.

Identification—

A: To 5 ml. of a warm solution of Ferrous Gluconate (1 in 10) add 0.65 ml. of glacial acetic acid and 1 ml. of freshly distilled phenylhydrazine, and heat the mixture on a steam bath for 30 minutes. Cool the mixture, and scratch the inner surface of the container with a glass stirring rod: crystals of gluconic acid phenylhydrazide form.

B: A solution of Ferrous Gluconate (1 in 20) responds to the tests for *Ferrous salts*, page 809.

Loss on drying, page 814—Dry Ferrous Gluconate at 105° for 4 hours: it loses not less than 6.5 percent and not more than 10 percent of its weight.

Chloride, page 784—One g. of Ferrous Gluconate shows no more chloride than corresponds to 1 ml. of 0.02 *N* hydrochloric acid (0.07 percent).

Sulfate, page 784—One g. of Ferrous Gluconate shows no more sulfate than corresponds to 1 ml. of 0.02 *N* sulfuric acid (0.1 percent).

Oxalic acid—Dissolve 1 g. of Ferrous Gluconate in 10 ml. of water, add 2 ml. of hydrochloric acid, and transfer to a separator. Extract successively with 50 and 20 ml. of ether. Combine the ether extracts, add 10 ml. of water, and evaporate the ether on a steam bath. Add 1 drop of acetic acid and 1 ml. of calcium acetate solution (1 in 20): no turbidity is produced within 5 minutes.

Ferric iron—Dissolve about 5 g. of Ferrous Gluconate, accurately weighed, in a mixture of 100 ml. of water and 10 ml. of hydrochloric acid, and add 3 g. of potassium iodide. Shake well, and allow to stand in the dark for 5 minutes. Titrate any liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 5.585 mg. of ferric iron. Ferrous Gluconate contains not more than 2 percent of ferric iron.

Reducing sugars—Dissolve 500 mg. of Ferrous Gluconate in 10 ml. of water, warm, and make alkaline with 1 ml. of ammonia T.S. Pass hydrogen sulfide gas into the solution to precipitate the iron, and permit the solution to stand for 30 minutes to coagulate the precipitate. Filter, and wash the precipitate with two successive 5-ml. portions of water. Acidify the combined filtrate and washings with hydrochloric acid, and add 2 ml. of diluted hydrochloric acid in excess. Boil the solution until the vapors no longer darken lead acetate paper, and continue to boil, if necessary, until it has been concentrated to about 10 ml. Cool, add 5 ml. of sodium carbonate T.S. and 20 ml. of water, filter, and adjust the volume of the filtrate to 100 ml. To 5 ml. of the filtrate add 2 ml. of alkaline cupric tartrate T.S., and boil for 1 minute: no red precipitate is formed within 1 minute.

Assay—Dissolve about 1.5 g. of Ferrous Gluconate, previously dried at 105° for 4 hours and accurately weighed, in a mixture of 75 ml. of water and 15 ml. of diluted sulfuric acid in a 300-ml. conical flask. Add 250 mg. of zinc dust, close the flask with a stopper containing a Bunsen valve, and allow to stand at room temperature for 20 minutes or until the solution becomes colorless. Filter the solution through a Gooch crucible containing an asbestos mat coated with a thin layer of zinc dust, and wash the crucible and contents with 10 ml. of diluted sulfuric acid, followed by 10 ml. of water. Add orthophenanthroline T.S., and titrate the filtrate in the suction flask immediately with 0.1 *N* ceric sulfate. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* ceric sulfate is equivalent to 44.62 mg. of $C_{12}H_{22}FeO_{14}$.

Packaging and storage—Preserve Ferrous Gluconate in tight containers.

Category—Iron supplement.
Usual dose—**300 mg.** three times a day.
Usual dose range—**200** to **600 mg.**

Ferrous Gluconate Tablets

Ferrous Gluconate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{12}H_{22}FeO_{14}.2H_2O$.

Identification—Dissolve a quantity of powdered Ferrous Gluconate Tablets, equivalent to about 1 g. of ferrous gluconate, in 10 ml. of water, and filter: the solution responds to the *Identification tests* under *Ferrous Gluconate*, page 304.

Disintegration, page 878—The disintegration time limit for Ferrous Gluconate Tablets is 60 minutes.

Weight variation, page 901—Ferrous Gluconate Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Ferrous Gluconate Tablets. Weigh accurately a portion of the powder, equivalent to about 1.5 g. of ferrous gluconate, and dissolve it in a mixture of 75 ml. of water and 15 ml. of diluted sulfuric acid contained in a 300-ml. conical flask. Proceed as directed in the *Assay* under *Ferrous Gluconate*, page 304, beginning with "Add 250 mg. of zinc dust. . . ." Each ml. of 0.1 *N* ceric sulfate is equivalent to 48.22 mg. of $C_{12}H_{22}FeO_{14}.2H_2O$.

Packaging and storage—Preserve Ferrous Gluconate Tablets in tight containers.

Tablets available—Ferrous Gluconate Tablets usually available contain the following amount of ferrous gluconate: 300 mg.

Category and Dose—See Ferrous Gluconate.

Ferrous Sulfate Syrup

Ferrous Sulfate Syrup contains, in each 100 ml., not less than 3.75 g. and not more than 4.25 g. of $FeSO_4.7H_2O$.

Ferrous Sulfate	40	g.
Citric Acid, hydrous	2.1	g.
Peppermint Spirit	2	ml.
Sucrose	825	g.
Purified Water, a sufficient quantity,		
To make	1000	ml.

Dissolve the ferrous sulfate, the citric acid, the peppermint spirit, and 200 g. of sucrose in 450 ml. of purified water, and filter the solution until clear. Then dissolve the remainder of the sucrose in the clear filtrate, and add sufficient purified water to make 1000 ml. Mix well, and filter, if necessary, through a pledget of cotton.

Assay—Transfer 25 ml. of Ferrous Sulfate Syrup, accurately measured, to a 250-ml. conical flask. Add 15 ml. of diluted sulfuric acid and 100 ml. of water, and shake well. Add 3 drops of orthophenanthroline T.S., and titrate with 0.1 *N* ceric sulfate. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* ceric sulfate is equivalent to 27.80 mg. of $FeSO_4.7H_2O$.

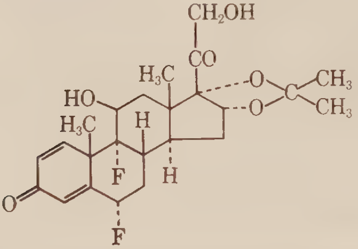
Packaging and storage—Preserve Ferrous Sulfate Syrup in tight containers.

Category—Iron supplement.

Usual dose—**10 ml.**

One usual dose contains about 400 mg. of ferrous sulfate.

Fluocinolone Acetonide*



6α,9α-Difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, Cyclic 16,17-Acetal with Acetone

$C_{24}H_{30}F_2O_6$ Mol. wt. 452.50

Fluocinolone Acetonide contains not less than 97.0 percent and not more than 103.0 percent of $C_{24}H_{30}F_2O_6$, calculated on the dried basis.

Description—Fluocinolone Acetonide occurs as a white or practically white, odorless, crystalline powder. It is stable in air, and when tested by the method for *Class Ia,* page 815, it melts at about 270° with decomposition.

Solubility—Fluocinolone Acetonide is insoluble in water. It is soluble in methanol and is slightly soluble in ether and in chloroform.

Identification—Prepare a solution of Fluocinolone Acetonide in chloroform containing 500 mcg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution and 10 μl. of a chloroform solution of NF Fluocinolone Acetonide Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and diethylamine (2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Fluocinolone Acetonide, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Fluocinolone Acetonide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Fluocinolone Acetonide in methanol exhibits maxima and minima at the same wavelengths as that of NF Fluocinolone Acetonide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 238 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Fluocinolone Acetonide, calculated on the dried basis, determined in a solution in methanol containing 100 mg. of Fluocinolone Acetonide in each 10 ml., is between +98° and +108°.

Loss on drying, page 814—Dry Fluocinolone Acetonide at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 100 mg. of Fluocinolone Acetonide is negligible.

Foreign steroids and other impurities—*Standard preparation*—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Fluocinolone Acetonide Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Fluocinolone Acetonide, previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for

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* Patented. See notice, page ii.

Procedure under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of methanol and chloroform (95:5) and determining the absorbance at the maximum at about 238 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg. of Fluocinolone Acetonide taken: not more than 3 percent is found.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay,* page 876, using NF Fluocinolone Acetonide Reference Standard.

Assay preparation—Weigh accurately about 100 mg. of Fluocinolone Acetonide, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Pipet 5.0 ml. of this solution into a 250 ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered 50-ml. conical flask.

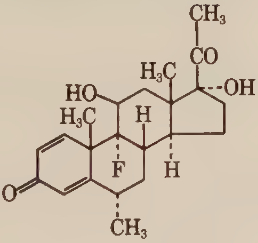
Procedure—Proceed as directed under *Steroid Assay,* page 876, except allow to stand in the dark for 45 minutes. Calculate the quantity, in mg., of $C_{24}H_{30}F_2O_6$ in the portion of Fluocinolone Acetonide taken by the formula $10C \times (A_U/A_S)$.

Packaging and storage—Preserve Fluocinolone Acetonide in well-closed containers.

CATEGORY—Glucocorticoid.

FOR EXTERNAL USE—Topically as a 0.01 to 0.2 percent cream, ointment or solution.

Fluorometholone*



9-Fluoro-11β,17-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione

$C_{22}H_{29}FO_4$ Mol. wt. 376.47

Fluorometholone contains not less than 97.0 percent and not more than 103.0 percent of $C_{22}H_{29}FO_4$, calculated on the dried basis.

Description—Fluorometholone occurs as a white to yellowish white, odorless, crystalline powder. When tested by the method for *Class Ia,* page 815, it melts at about 280° with some decomposition.

Solubility—Fluorometholone is practically insoluble in water. It is slightly soluble in alcohol and is very slightly soluble in chloroform and in ether.

Identification—Prepare a solution of Fluorometholone in methanol containing 500 mcg. per ml. On a suitable thin-layer chromatographic plate (page 871), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 100 μl. of this solution and 100 μl. of a methanol solution of NF Fluorometholone Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of methylene chloride and acetone (4:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under short-wave ultraviolet light: the R_f value of the main spot obtained from the sample solution corresponds to that obtained with the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Fluorometholone, previously dried at 60° in vacuum for 3 hours, exhibits maxima only at the same wavelengths as that of NF Fluorometholone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Fluorometholone in methanol exhibits maxima and minima at the same wavelengths as that of NF Fluorometholone Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 239 mμ, do not differ by more than 3 percent.

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* Patented. See notice, page ii.

Specific rotation, page 822—The specific rotation of Fluorometholone, calculated on the dried basis, determined in a solution in pyridine containing 100 mg. of Fluorometholone in each 10 ml., is between +52° and +60°.

Loss on drying, page 814—Dry Fluorometholone at 60° in vacuum for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Fluorometholone yields not more than 0.2 percent of residue on ignition.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Fluorometholone Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Fluorometholone previously dried at 60° in vacuum for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and acetone (4:1), and determining the absorbance at the maximum at about 239 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Fluorometholone taken: not more than 3 percent is found.

Assay—

Standard preparation—Dissolve in alcohol a suitable quantity of NF Fluorometholone Reference Standard, previously dried at 60° in vacuum for 3 hours and accurately weighed, and dilute quantitatively and stepwise with alcohol to obtain a solution having a concentration of about 20 mcg. per ml.

Assay preparation—Weigh accurately about 100 mg. of Fluorometholone, dissolve in sufficient alcohol to make 200.0 ml., and mix. Pipet 10.0 ml. of this solution into a 250-ml. volumetric flask, dilute to volume with alcohol, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 50-ml. glass-stoppered conical flasks, and evaporate to dryness on a steam bath. To each flask, and to a similar flask to provide the blank, add 15.0 ml. of a solution of 250 mg. of isoniazid and 0.3 ml. of hydrochloric acid in 500 ml. of methanol. Rotate the flasks to dissolve all residue remaining from the evaporation, and allow to stand in a water bath at 40° for 1 hour. Cool to room temperature, and determine the absorbances of the solutions obtained from the *Assay preparation* and the *Standard preparation*, in 1-cm. cells, at the maximum at about 410 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Assay preparation* as A_U and that from the *Standard preparation* as A_S. Calculate the quantity, in mg., of $C_{22}H_{29}FO_4$ in the portion of Fluorometholone taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Fluorometholone in tight, light-resistant containers.

Category—Glucocorticoid.

For external use—Topically, as a 0.025 percent cream one to three times a day.

Fluorometholone Cream

Fluorometholone Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{29}FO_4$.

Identification—Transfer a quantity of Fluorometholone Cream, equivalent to about 1 mg. of fluorometholone, to a separator, disperse in 5 ml. of water, and extract with 10 ml. of chloroform. Remove the chloroform layer, evaporate to dryness, and dissolve the residue in 2.0 ml. of methanol. Proceed as directed for *Identification* under *Fluorometholone*, page 307, beginning with "On a suitable thin-layer chromatographic plate . . . ."

Weight variation, page 901—Fluorometholone Cream meets the requirements of the weight variation test for creams.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Fluorometholone*, page 307.

Assay preparation—Transfer an accurately weighed portion of Fluorometholone Cream, equivalent to about 500 mcg. of fluorometholone, to a 100-ml. volumetric flask, add 40 ml. of methanol, heat to boiling in a water bath, and agitate to assure complete solution of the fluorometholone. Cool to room temperature, dilute to volume with methanol, and mix. Cool this solution in ice water for 30 minutes, filter the chilled solution, and allow the filtrate to return to room temperature. Use the filtrate as directed in the *Procedure.*

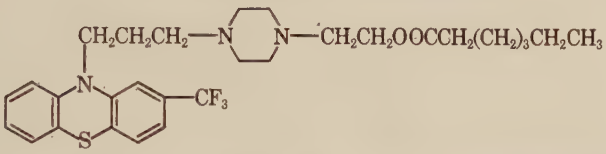
Procedure—Transfer 5.0 ml. of the *Standard preparation* and 20.0 ml. of the *Assay preparation* to separate 50-ml. glass-stoppered conical flasks, evaporate to dryness on a steam bath, and proceed as directed for *Procedure* in the *Assay* under *Fluorometholone*, page 307. Calculate the quantity, in mg., of $C_{22}H_{29}FO_4$ in the portion of Fluorometholone Cream taken by the formula $0.025C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Fluorometholone Cream in collapsible tubes.

Cream available—Fluorometholone Cream is usually available in the following concentration: 0.025 percent.

Category and Application—See Fluorometholone.

Fluphenazine Enanthate*



4-[3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl]-1-piperazineethanol Heptanoate (ester)

$C_{29}H_{38}F_3N_3O_2S$ Mol. wt. 549.70

Fluphenazine Enanthate contains not less than 97.0 percent and not more than 103.0 percent of $C_{29}H_{38}F_3N_3O_2S$, calculated on the dried basis.

Description—Fluphenazine Enanthate occurs as a pale yellow to yellow-orange, clear to slightly turbid, viscous liquid. It has a characteristic odor. It is unstable in strong light, but stable to air at room temperature.

Solubility—Fluphenazine Enanthate is insoluble in water. It is freely soluble in alcohol, in chloroform, and in ether.

Identification—Dissolve 50 mg. of Fluphenazine Enanthate in 2 ml. of methanol, and add 3 ml. of palladium chloride solution (1 in 1000): a rusty-red color is produced. Add an excess of the palladium chloride solution: the color intensifies to a brownish red.

Loss on drying, page 814—Dry Fluphenazine Enanthate in vacuum at 60° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Fluphenazine Enanthate yields not more than 0.2 percent of residue on ignition. Retain the residue from a 1-g. sample for the *Heavy metals test.*

Heavy metals, page 806—Dissolve the residue resulting from the *Residue on ignition test* in 23 ml. of water and 2 ml. of diluted acetic acid: the heavy metals limit for Fluphenazine Enanthate is 30 parts per million.

Assay—Dissolve about 500 mg. of Fluphenazine Enanthate, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 27.49 mg. of $C_{29}H_{38}F_3N_3O_2S$.

Packaging and storage—Preserve Fluphenazine Enanthate in tight, light-resistant containers.

Category—Tranquilizer (major).

Usual dose—Intramuscular or subcutaneous, **25 mg.** every 2 weeks.

Usual dose range—**12.5** to **100 mg.**

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* Patented. See notice, page ii.

Fluphenazine Enanthate Injection

Fluphenazine Enanthate Injection is a sterile solution of fluphenazine enanthate in a suitable vegetable oil. It contains not less than 90.0 percent and not more than 125.0 percent of the labeled amount of $C_{29}H_{38}F_3N_3O_2S$.

Identification—A volume of Fluphenazine Enanthate Injection, equivalent to about 50 mg. of fluphenazine enanthate, responds to the *Identification test* under *Fluphenazine Enanthate,* page 309.

Other requirements—Fluphenazine Enanthate Injection meets the requirements under *Injections,* page 810.

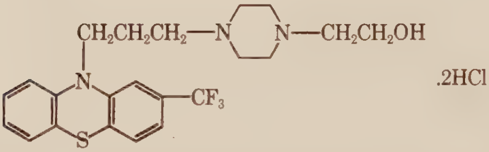
Assay—Dissolve an accurately measured volume of Fluphenazine Enanthate Injection, equivalent to about 150 mg. of fluphenazine enanthate, in 75 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 27.49 mg. of $C_{29}H_{38}F_3N_3O_2S$.

Packaging and storage—Preserve Fluphenazine Enanthate Injection in single-dose or in multiple-dose containers, preferably of Type I or Type III glass.

Injections available—Fluphenazine Enanthate Injection usually available contains the following amounts of fluphenazine enanthate: 25 mg. in 1 ml.; 125 mg. in 5 ml., and 250 mg. in 10 ml.

CATEGORY and DOSE—See Fluphenazine Enanthate.

Fluphenazine Hydrochloride*



4-[3-[2-(Trifluoromethyl)phenothiazin-10-yl]propyl]-1-piperazineethanol Dihydrochloride

$C_{22}H_{26}F_3N_3OS.2HCl$ Mol. wt. 510.45

Fluphenazine Hydrochloride, dried at 65° for 3 hours, contains not less than 97.0 percent and not more than 103.0 percent of $C_{22}H_{26}F_3N_3OS.2HCl$.

Description—Fluphenazine Hydrochloride occurs as a white or nearly white odorless, crystalline powder. It melts within a range of 5° above 225°.

Solubility—Fluphenazine Hydrochloride is freely soluble in water. It is slightly soluble in acetone, in alcohol, and in chloroform. It is practically insoluble in benzene and in ether.

Identification—

A: Dissolve about 5 mg. of Fluphenazine Hydrochloride in 5 ml. of methanol and add cautiously 2 ml. of sulfuric acid: a pink color is produced. Add 1 drop of ferric ammonium sulfate T.S.: the color changes to reddish purple.

B: A solution of Fluphenazine Hydrochloride responds to the test for *Chloride,* page 808.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Fluphenazine Hydrochloride, previously dried at 65° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Fluphenazine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Fluphenazine Hydrochloride in methanol exhibits maxima and minima at the same wavelengths as that of NF Fluphenazine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 259 mμ, do not differ by more than 2.5 percent.

Loss on drying, page 814—Dry Fluphenazine Hydrochloride at 65° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Fluphenazine Hydrochloride yields not more than 0.5 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Fluphenazine Hydrochloride is 30 parts per million.

Assay—Dissolve about 500 mg. of Fluphenazine Hydrochloride, previously dried at 65° for 3 hours and accurately weighed, in a mixture of 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., warming slightly if necessary to effect solution. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 25.52 mg. of $C_{22}H_{26}F_3N_3OS.2HCl$.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Fluphenazine Hydrochloride in tight, light-resistant containers.

CATEGORY—Tranquilizer (major).

USUAL DOSE RANGE—**0.5** to **2 mg.** daily.

Fluphenazine Hydrochloride Injection*

Fluphenazine Hydrochloride Injection is a sterile solution of fluphenazine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{26}F_3N_3OS.2HCl$.

Identification—

A: Transfer a volume of Fluphenazine Hydrochloride Injection, equivalent to about 5 mg. of fluphenazine hydrochloride to a test tube, add 8 ml. of water, and mix. Divide the solution into two 5-ml. portions. To one portion add 5 ml. of a mixture of equal volumes of nitric acid and water, and mix: a peach to amber color develops quickly, which turns dark brown, then suddenly changes to a clear solution with a yellow tint. To the other portion add 1 ml. of hydrochloric acid, and mix: the solution remains clear.

B: The ultraviolet absorption spectum of the *Assay preparation*, prepared as directed in the *Assay*, exhibits maxima and minima at the same wavelengths as that of the *Standard preparation*, similarly measured.

pH, page 824—The pH of Fluphenazine Hydrochloride Injection is between 4.8 and 5.2.

Other requirements—Fluphenazine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—

Solvent mixture—Wash 800 ml. of *n*-heptane with 200 ml. each of 1 *N* sodium hydroxide and of 1 *N* hydrochloric acid, followed by three 200-ml. portions of water. Wash 40 ml. of isoamyl alcohol with 10 ml. each of 1 *N* sodium hydroxide and of 1 *N* hydrochloric acid, followed by three 10-ml. portions of water. Prepare a 97:3 mixture of the washed *n*-heptane and isoamyl alcohol.

pH 5.6 buffer—Adjust the pH of 0.1 *M* sodium acetate to 5.6 using glacial acetic acid.

Standard preparation—Transfer about 35 mg. of NF Fluphenazine Hydrochloride Reference Standard, accurately weighed, to a 50-ml. volumetric flask, add water to volume, and mix.

Assay preparation—Transfer an accurately measured volume of Fluphenazine Hydrochloride Injection, equivalent to about 7.5 mg. of fluphenazine hydrochloride, to a 10-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Transfer 1.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate centrifuge bottles each containing 2 ml. of water. Treat each solution as follows: add 100.0 ml. of *Solvent mixture* followed by 1 ml. of sodium hydroxide solution (1 in 10), shake mechanically for 10 minutes, and centrifuge. Transfer 25.0 ml. of the organic phase to a second centrifuge bottle containing 5 ml. of *pH 5.6 buffer*, shake mechanically for 3 minutes, and centrifuge. Transfer 20.0 ml. of the organic phase from this bottle to a third centrifuge bottle containing 20.0 ml. of 0.5 *N* sulfuric acid, shake mechanically for 5 minutes, and centrifuge. Remove and discard the organic phase, and concomitantly determine the absorbances of the aqueous acid solutions in 1-cm. cells, at the maximum at about 255 mμ, with a suitable spectrophotometer, using 0.5 *N* sulfuric acid as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{26}F_3N_3OS.2HCl$ in each ml. of the Injection taken by the formula $0.01 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Fluphenazine Hydrochloride Injection in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

Injection available—Fluphenazine Hydrochloride Injection usually available contains the following amount of fluphenazine hydrochloride: 25 mg. in 10 ml.

CATEGORY and DOSE—See Fluphenazine Hydrochloride.

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* Patented. See notice, page ii.

Fluphenazine Hydrochloride Tablets*

Fluphenazine Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{26}F_3N_3OS \cdot 2HCl$.

Identification—Digest an amount of finely powdered Fluphenazine Hydrochloride Tablets, equivalent to about 5 mg. of fluphenazine hydrochloride, with 5 ml. of methanol, and filter: the filtrate responds to *Identification test A* under *Fluphenazine Hydrochloride*, page 310.

Disintegration—The disintegration time limit for Fluphenazine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Fluphenazine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Palladium chloride solution—Dissolve 500 mg. of palladium chloride in a mixture of 250 ml. of water and 5 ml. of hydrochloric acid, heating on a steam bath until solution is effected, cool, and dilute with water to 500 ml. Store in an amber bottle and use within 30 days. On the day of use, dilute 5 ml. of this solution and 9.6 ml. of 1 *N* hydrochloric acid to 100 ml. with water.

Standard preparation—Transfer about 50 mg. of NF Fluphenazine Hydrochloride Reference Standard, accurately weighed, to a 500-ml. volumetric flask, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a separator, add 1 ml. of sodium hydroxide solution (1 in 2), and extract with four 20-ml. portions of *n*-hexane. Filter the extracts through a pledget of glass wool into a 100-ml. volumetric flask. Dilute to volume with *n*-hexane and mix.

Assay preparation—Weigh and finely powder not less than 20 Fluphenazine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 1 mg. of fluphenazine hydrochloride, to a separator, add 10 ml. of water, and proceed as directed under *Standard preparation*, beginning with "... add 1 ml. of sodium hydroxide solution ... ."

Procedure—Extract 20.0 ml. each of the *Standard preparation* and of the *Assay preparation* with 4.0 ml. of *Palladium chloride solution*, and concomitantly determine the absorbance of each extract in 1-cm. cells, at the maximum at about 480 mμ, with a suitable spectrophotometer, using *Palladium chloride solution* as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{26}F_3N_3OS \cdot 2HCl$ in the portion of Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Fluphenazine Hydrochloride Tablets in tight containers.

Tablets available—Fluphenazine Hydrochloride Tablets usually available contain the following amounts of fluphenazine hydrochloride: 250 mcg., and 1, 2.5, 5, and 10 mg.

CATEGORY and DOSE—See Fluphenazine Hydrochloride.

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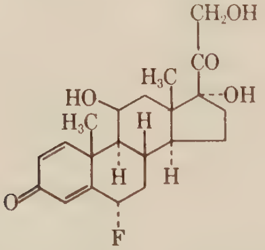
* Patented. See notice, page ii.

Fluprednisolone*



6α-Fluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione

$C_{21}H_{27}FO_5$ Mol. wt. 378.44

Fluprednisolone contains not less than 97.0 percent and not more than 103.0 percent of $C_{21}H_{27}FO_5$, calculated on the dried basis.

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* Patented. See notice, page ii.

Description—Fluprednisolone occurs as a white to off-white, odorless, crystalline powder.

Solubility—Fluprednisolone is sparingly soluble in alcohol, slightly soluble in chloroform and in ether, and practically insoluble in water.

Identification—Prepare a solution of Fluprednisolone in chloroform containing 500 mcg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 10 μl. of this solution and 10 μl. of a chloroform solution of NF Fluprednisolone Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of methylene chloride and acetone (4:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under shortwave ultraviolet light: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Fluprednisolone in alcohol exhibits maxima and minima at the same wavelengths as that of NF Fluprednisolone Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance occurring at about 242 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Fluprednisolone, calculated on the dried basis, determined in a solution of dioxane containing 100 mg. of Fluprednisolone in each 10 ml., is between +87° and +95°.

X-ray diffraction, page 902—The X-ray diffraction pattern of Fluprednisolone conforms to either one or a mixture of the patterns described by the following data:

Form A		Form B	
d	I/I_1	d	I/I_1
7.65	2	10.39	2
6.51	15	10.24	3
6.31	17	9.52	6
6.08	20	8.94	37
5.65	53	8.35	29
5.51	35	7.10	64
5.03	100	5.96	22
4.83	21	5.47	100
4.69	18	5.21	6
4.56	7	5.14	7
4.21	12	4.72	13
4.02	13	4.63	6
3.93	8	4.44	24
3.79	6	4.20	9
3.74	6	4.10	6
3.64	12	3.86	2
3.53	14	3.75	9
3.43	12	3.62	2
3.31	1	3.54	2
3.25	7	3.41	7
3.11	7	3.14	1
3.03	13	3.05	8
2.90	6	2.96	4
2.86	7	2.92	4
2.83	6	2.87	3
2.72	12	2.79	3
2.64	4	2.77	3
2.58	8	2.72	1
2.53	4	2.63	2
2.48	5	2.59	2
2.44	5	2.55	1
2.43	5	2.47	2
2.36	6	2.46	3
2.33	5	2.43	1
2.28	5	2.30	3
2.25	3		

Loss on drying, page 814—Dry Fluprednisolone at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Fluprednisolone yields not more than 0.2 percent of residue on ignition.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Fluprednisolone Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Fluprednisolone previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of benzene and acetone (4:1), and determining the absorbance at the maximum at about 242 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Fluprednisolone taken: not more than 3 percent is found.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay,* page 876, using NF Fluprednisolone Reference Standard.

Assay preparation—Weigh accurately about 100 mg. of Fluprednisolone, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Pipet 5.0 ml. of this solution into a 250-ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered 50-ml. conical flask.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{21}H_{27}FO_5$ in the portion of Fluprednisolone taken by the formula $10C \times (A_U/A_S)$.

Packaging and storage—Preserve Fluprednisolone in well-closed containers.

Category—Glucocorticoid.

Usual dose range—**750 mcg.** to **5.25 mg.** one to four times daily.

Fluprednisolone Tablets

Fluprednisolone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{27}FO_5$.

Identification—Evaporate 25 ml. of the *Assay preparation* from the *Assay* on a steam bath just to dryness, dissolve the residue in 1 ml. of chloroform, and proceed as directed for *Identification* under *Fluprednisolone*, page 312.

Disintegration, page 878—The disintegration time limit for Fluprednisolone Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Fluprednisolone Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using NF Fluprednisolone Reference Standard.

Assay preparation—Weigh and finely powder not less than 10 Fluprednisolone Tablets. Weigh accurately a portion of the powder, equivalent to about 5 mg. of fluprednisolone, and transfer with the aid of 10 ml. of water to a separator. Extract the fluprednisolone completely using four 25-ml. portions of chloroform, filtering each extract through chloroform-washed cotton into a 250-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 10.0 ml. of this solution into a glass-stoppered 50-ml. conical flask, evaporate the chloroform on a steam bath just to dryness, cool, and dissolve the residue in 20.0 ml. of alcohol.

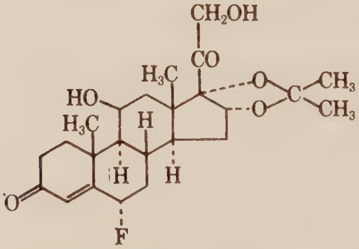
Procedure—Proceed as directed for *Procedure* under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{21}H_{27}FO_5$ in the portion of the tablets taken by the formula $0.5C \times (A_U/A_S)$.

Packaging and storage—Preserve Fluprednisolone Tablets in well-closed containers.

Tablets available—Fluprednisolone Tablets usually available contain the following amounts of fluprednisolone: 750 mcg. and 1.5 mg.

Category and Dose—See Fluprednisolone.

Flurandrenolide*



6α-Fluoro-11β,16α,17,21-tetrahydroxypregn-4-ene-3,20-dione, Cyclic 16,17-Acetal with Acetone

$C_{24}H_{33}FO_6$ Mol. wt. 436.53

Flurandrenolide contains not less than 95.0 percent and not more than 102.0 percent of $C_{24}H_{33}FO_6$, calculated on the dried basis.

Description—Flurandrenolide occurs as a white to off-white, fluffy, crystalline powder. It is odorless.

Solubility—Flurandrenolide is freely soluble in chloroform, soluble in methanol, and sparingly soluble in alcohol. It is practically insoluble in water and in ether.

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* Patented. See notice, page ii.

Identification—Line the inside of a chromatographic chamber suitable for descending chromatography (see page 789) with Whatman No. 1 or equivalent filter paper. Fill the solvent trough with benzene previously saturated with formamide to serve as the mobile phase, and also place sufficient of the same liquid on the bottom of the chamber to permit the liner to be in contact with it. Allow the chamber to equilibrate for 16 hours. Prepare a strip of filter paper, about 15 × 46 cm., draw a line across the narrow dimension about 6 cm. from one end, and mark two points for application of solutions along this line about 3.5 cm. from each edge of the paper. Immerse the strip in a mixture of acetone and formamide (2:1), blot, and air-dry at room temperature. Spot 10 μl. of a 1 in 100 solution of Flurandrenolide in chloroform-methanol (1:1) at one application point, and similarly spot 10 μl. of a 1 in 100 solution of NF Flurandrenolide Reference Standard at another application point. Suspend the strip in the chamber, and allow to develop until the solvent front is within 2.5 to 3 cm. of the bottom of the paper (about 3.5 hours). Remove the strip, mark the solvent front, and air-dry the strip in a hood at room temperature overnight. Spray the strip with a 2:1 mixture of blue tetrazolium solution (1 in 500) and sodium hydroxide solution (1 in 10), circle all purplish spots with a soft-lead pencil while the paper is still wet, and then air-dry the chromatogram at room temperature in a hood: the spots produced by the sample solution correspond in pattern and intensity to those produced by the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 20 solution of Flurandrenolide, previously dried in vacuum at 105° for 4 hours, in chloroform exhibits maxima only at the same wavelengths as that of NF Flurandrenolide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 25,000 solution of Flurandrenolide in methanol exhibits maxima and minima at the same wavelengths as that of NF Flurandrenolide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 237 mμ, do not differ by more than about 3 percent.

Specific rotation, page 822—The specific rotation of Flurandrenolide, previously dried in vacuum at 105° for 4 hours, determined in a solution in chloroform containing 100 mg. of Flurandrenolide in each 10 ml. is between +140° and +150°.

X-ray diffraction, page 902—The X-ray diffraction pattern of Flurandrenolide conforms to either one or a mixture of the patterns described by the following data:

Form A		Form B	
d	I/I_1	d	I/I_1
10.64	40	10.58	20
9.11	20	8.53	40
7.62	30	7.60	2
6.41	30	7.27	100
6.13	15	6.77	2
5.73	100	6.29	60
5.35	70	5.65	80
5.14	80	5.30	20
4.75	5	4.87	50
4.57	10	4.53	10
4.14	60	4.19	4
4.02	5	3.82	40
3.87	70	3.66	20
3.68	30	3.47	15
3.47	20	3.28	2
3.21	8b	3.03	2
3.07	8b	2.85	4
2.98	4	2.62	2
2.91	4	2.49	2
2.84	8	2.34	2
2.79	6	2.25	1
2.71	15	2.11	1
2.66	4	2.04	1
2.59	6	1.95	1
2.48	15	1.88	1
2.37	6b		
2.20	4b		
2.13	4		
2.08	8		
2.06	6		

Loss on drying, page 814—Dry Flurandrenolide in vacuum at 105° for 4 hours: it loses not more than 1 percent of its weight.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Flurandrenolide Reference Standard to prepare a solution containing approximately 10 mg. per ml.

Test preparation—Weigh accurately about 50 mg. of Flurandrenolide, previously dried in vacuum at 105° for 4 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 5.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, applying 10 μl. each of the *Test Preparation* and of the *Standard Preparation* to the chromatographic plate (previously activated by heating at 110° for 1 hour), and using a solvent system consisting of benzene and ethyl acetate (1:1). Determine the absorbances at the maximum at about 237 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 5 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the

Standard preparation, and W is the weight, in mg., of Flurandrenolide taken: not more than 3 percent is found.

Assay—

Blue tetrazolium solution—Dissolve 75 mg. of blue tetrazolium in 50 ml. of a 1 in 10 solution of water in dehydrated alcohol, and mix.

Tetramethylammonium hydroxide solution—Dilute 10.0 ml. of tetramethylammonium hydroxide (1 in 10) with sufficient dehydrated alcohol to make 50.0 ml., and mix.

Standard preparation—Transfer about 10 mg. of NF Flurandrenolide Reference Standard, accurately weighed, to a 100-ml. volumetric flask, dissolve in dehydrated alcohol, dilute to volume with dehydrated alcohol, and mix. Transfer 10.0 ml. of the solution to a 50-ml. volumetric flask, dilute to volume with dehydrated alcohol, and mix. Transfer 10.0 ml. of this solution to a 25-ml. volumetric flask, dilute to volume with dehydrated alcohol, and mix.

Assay preparation—Prepare from Flurandrenolide as directed under *Standard preparation.*

Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 10-ml. volumetric flasks, and transfer 5.0 ml. of dehydrated alcohol to a third flask to serve as the reagent blank. To each flask add 1.0 ml. of *Blue tetrazolium solution*, mix, heat in a water bath at 39° to 41°, swirling occasionally, and then, after 5.0 minutes, add 1.0 ml. of *Tetramethylammonium hydroxide solution*, and mix. Remove each flask from the water bath 10.0 minutes after addition of the latter reagent, allow to stand at room temperature for 5.0 minutes, dilute to volume with glacial acetic acid, and mix. Five minutes after the addition of the glacial acetic acid, concomitantly determine the absorbance of each solution, in 1-cm. cells, at the maximum at about 520 mμ, with a suitable spectrophotometer, using the reagent blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{24}H_{33}FO_6$ in the Flurandrenolide taken by the formula $1.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Flurandrenolide in tight containers in a cold place, protected from light.

Category—Glucocorticoid.

For External Use—Topically, as a **0.025** or **0.05 percent** cream or ointment to the affected area two or three times a day.

Flurandrenolide Cream*

Flurandrenolide Cream contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{33}FO_6$.

Identification—The *Assay preparation*, treated as directed for *Procedure* in the *Assay*, exhibits an absorbance maximum at about 520 mμ.

Weight variation, page 901—Flurandrenolide Cream meets the requirements of the weight variation test for creams.

Assay—

Blue tetrazolium solution and *Tetramethylammonium hydroxide solution*—Prepare as directed in the *Assay* under *Flurandrenolide* page 314.

Acetic acid-chloroform (1 in 200)—Wash chloroform with water to remove completely any alcohol that may be present, and dry over anhydrous sodium sulfate. Transfer 5.0 ml. of glacial acetic acid to a 1000-ml. volumetric flask, dilute to volume with the washed and dried chloroform, and mix.

Alcohol-chloroform (1 in 200)—Wash chloroform with water to remove completely any alcohol that may be present, and dry over anhydrous sodium sulfate. Transfer 5.0 ml. of dehydrated alcohol to a 1000-ml. volumetric flask, dilute to volume with the washed and dried chloroform, and mix.

Alcohol-chloroform (1 in 20)—Transfer 5.0 ml. of dehydrated alcohol to a 100-ml. volumetric flask, dilute to volume with *Alcohol-chloroform (1 in 200)*, and mix.

Adsorbent—Slowly add, with constant stirring, chromatographic magnesium silicate to a beaker containing a slightly larger volume of hydrochloric acid than the chromatographic magnesium silicate to be treated, boil on a steam bath for 15 minutes, stirring frequently to prevent spattering. Insert into the stem of a glass funnel a pledget of glass wool that has previously been washed successively with hydrochloric acid, water, dehydrated alcohol, and *Alcohol-chloroform (1 in 200)*. Place a short length of vinyl tubing equipped with a screw clamp over the stem of the funnel, close the clamp, and add sufficient hydrochloric acid through the funnel to fill the stem. Transfer the adsorbent slurry to the funnel, and release the clamp. Wash the chromatographic magnesium silicate in the funnel with hydrochloric acid until the yellow color is removed and the washings are colorless, then wash with water until free from chloride, and finally wash with dehydrated alcohol followed by *Alcohol-chloroform (1 in 200)*. Dry at 100° for 16 hours, and store in a tight container.

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* Patented. See notice, page ii.

Chromatographic columns—Pack pledgets of glass wool, previously washed as described under *Adsorbent*, at the base of 1.2 × 30-cm. chromatographic tubes equipped with stopcocks. Add to each tube a slurry prepared by mixing 4 g. of *Adsorbent* with *Alcohol-chloroform (1 in 200)*, taking precautions to prevent the formation of air pockets or channels. Wash down the sides of the tubes with *Alcohol-chloroform (1 in 200)*, allow the adsorbent to settle, and tap the tubes gently and uniformly. Insert a pledget of the previously washed glass wool in the top of each tube. (*Caution:* Do not allow the top of the adsorbent to become dry during the preparation of the columns.)

Standard preparation—Transfer about 10 mg. of NF Flurandrenolide Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add *Alcohol-chloroform (1 in 200)* to volume, dissolve, and mix. Transfer 10.0 ml. of this solution to a 50-ml. glass-stoppered flask, add 20 ml. of *Alcohol-chloroform (1 in 200)*, and continue as directed under *Assay preparation*, beginning with "Filter into a 50-ml. volumetric flask . . . ."

Assay preparation—Transfer an accurately weighed portion of Flurandrenolide Cream, equivalent to about 1 mg. of flurandrenolide, to a 50-ml. glass-stoppered flask, add 30 ml. of *Alcohol-chloroform (1 in 200)*, stopper, and stir mechanically for 10 minutes. Filter into a 50-ml. volumetric flask through a coarse-porosity sintered-glass funnel containing 20 g. of anhydrous sodium sulfate. Wash the sodium sulfate with several small portions of *Alcohol-chloroform (1 in 200)*, dilute to volume with *Alcohol-Chloroform (1 in 200)*, and mix. Add 10.0 ml. of this solution to the top of a chromatographic column, and adjust the flow rate of the column to about 50 drops per minute. When the last of the solution just enters the column, add two 2-ml. portions of *Acetic acid-chloroform (1 in 200)*, allow each portion to drain into the column, and add 40 ml. more of *Acetic acid-chloroform (1 in 200)*. When this disappears into the column, add 2.0 ml. of *Alcohol-chloroform (1 in 20)*, and allow this solution to drain into the column. Discard all column washings. Place a 25-ml. volumetric flask under the column, and continue adding *Alcohol-chloroform (1 in 20)* until the eluate has filled the flask to the mark, stopper the flask, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate 10-ml. volumetric flasks, and transfer 5.0 ml. of *Alcohol-chloroform (1 in 20)* to a third flask to serve as the reagent blank. Using mild heat and a stream of air, evaporate the contents of each flask nearly to dryness, remove from the heat, and complete the evaporation to dryness with the stream of air until the odor of acetic acid is no longer perceptible. Dissolve each residue in 5.0 ml. of dehydrated alcohol, then add to each flask 1.0 ml. of *Blue tetrazolium solution*, mix, and continue as directed in the *Assay* under *Flurandrenolide*, page 314, beginning with "... heat in a water bath at 39° to 41° . . . ." Calculate the quantity, in mg., of $C_{24}H_{33}FO_6$ in the portion of the Cream taken by the formula $0.125C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Flurandrenolide Cream in tight containers, protected from light.

Creams available—Flurandrenolide Cream usually available contains 0.025 percent or 0.05 percent of flurandrenolide.

Category and Application—See Flurandrenolide.

Flurandrenolide Ointment*

Flurandrenolide Ointment contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{33}FO_6$.

Identification—The *Assay preparation*, treated as directed for *Procedure* in the *Assay*, exhibits an absorbance maximum at about 520 mμ.

Weight variation, page 901—Flurandrenolide Ointment meets the requirements of the weight variation test for ointments.

Assay—

Blue tetrazolium solution and *Tetramethylammonium hydroxide solution*—Prepare as directed in the *Assay* under *Flurandrenolide*, page 314.

Alcohol-chloroform (1 in 200), Alcohol-chloroform (1 in 20), Adsorbent, and *Chromatographic columns*—Prepare as directed in the *Assay* under *Flurandrenolide Cream*, page 316.

Standard preparation—Transfer about 10 mg. of NF Flurandrenolide Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add dehydrated alcohol to volume, dissolve, and mix. Transfer 10.0 ml. of this solution to a 250-ml. separator containing 75 ml. of dehydrated alcohol and continue as directed under *Assay*

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* Patented. See notice, page ii.

preparation, beginning with "... and then add to the separator 1.0 ml. of 0.5 *N* hydrochloric acid and 150 ml. of water."

Assay preparation—Transfer an accurately weighed portion of Flurandrenolide Ointment, equivalent to about 1 mg. of flurandrenolide, to a 125-ml. conical flask, add 25 ml. of dehydrated alcohol, and heat on a steam bath until the sample has liquefied. Place a magnetic stirring bar in the flask, and stir for 5 minutes, heating the flask at intervals to keep the contents in a semi-liquid state. Cool to 10° in an ice water bath, and decant the alcohol solution through Whatman No. 1 or equivalent filter paper, collecting the filtrate in a 250-ml. separator. Treat the ointment remaining in the flask with two additional 25-ml. portions of dehydrated alcohol, in the same manner, filtering each solution into the separator. Wash the filter with two 5-ml. portions of dehydrated alcohol, add the washings to the separator, and then add to the separator 1.0 ml. of 0.5 *N* hydrochloric acid and 150 ml. of water. Extract with 25 ml. of *Alcohol-chloroform (1 in 200)*, shaking for 3 minutes, and filter the chloroform layer into a 100-ml. volumetric flask through a coarse-porosity sintered-glass funnel containing 20 g. of anhydrous sodium sulfate. Extract with two additional 25-ml. portions of *Alcohol-chloroform (1 in 200)*, filtering each into the flask, and wash the sodium sulfate and funnel with several small portions of *Alcohol-chloroform (1 in 200)*, dilute to volume with *Alcohol-chloroform (1 in 200)*, and mix. Transfer 20.0 ml. of this solution to a 50-ml. conical flask, evaporate the contents of the flask to dryness using mild heat and a stream of air, and dissolve the residue in 6 ml. of *Alcohol-chloroform (1 in 200)*. Add this solution to the top of a chromatographic column, rinsing the flask with two 2.0-ml. portions of *Alcohol-chloroform (1 in 200)* and adding the washings to the column. Adjust the flow rate of the column to about 50 drops per minute. When the last of the solution just enters the column, add two additional 2.0-ml. portions of *Alcohol-chloroform (1 in 200)*, allow each portion to drain into the column, and then add 30 ml. more of *Alcohol-chloroform (1 in 200)*. When this disappears into the column, add 2.0 ml. of *Alcohol-chloroform (1 in 20)*, and allow it to drain into the column. Discard all washings. Place a 25-ml. volumetric flask under the column, and continue adding *Alcohol-chloroform (1 in 20)* until the eluate has filled the flask to the mark, stopper the flask, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Flurandrenolide Cream*, page 316. Calculate the quantity, in mg., of $C_{24}H_{33}FO_6$ in the portion of Ointment taken by the formula $0.125C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Flurandrenolide Ointment in tight containers, protected from light.

Ointments available—Flurandrenolide Ointment usually available contains 0.025 percent or 0.05 percent of flurandrenolide.

Category and Application—See Flurandrenolide.

Flurothyl*

$CF_3CH_2—O—CH_2CF_3$

Bis(2,2,2-trifluoroethyl) Ether

$C_4H_4F_6O$ Mol. wt. 182.07

Flurothyl contains not less than 99.6 percent and not more than 100.0 percent of $C_4H_4F_6O$.

Caution—Flurothyl is volatile and flammable. Inhalation of vapors can produce convulsions.

Description—Flurothyl occurs as a clear, colorless, volatile liquid having a pleasant, mild, ethereal odor. It boils at about 64°.

Solubility—Flurothyl is slightly soluble in water. It is miscible with alcohol, with ether, with propylene glycol, and with halogenated solvents.

Specific gravity, page 866—The specific gravity of Flurothyl is not less than 1.415 and not more than 1.419 at 20°.

Refractive index, page 858—The refractive index of Flurothyl is not less than 1.279 and not greater than 1.281 at 20°.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 50 solution of Flurothyl in chloroform exhibits maxima at the following wavelengths, in μ: 6.85 (*w*), 6.95 (*w*), 7.10 (*w*), 7.65 (*m*), 7.80 (*s*), 8.55 (*s*), 8.85 (*m*), 9.95 (*m*), 10.30 (*w*), and 12.00 (*w*).

Ultraviolet absorption, page 866—Record the ultraviolet absorption spectrum of Flurothyl, in a 1-cm. cell, with a suitable spectrophotometer, from 220 mμ to 346 mμ, using water as the blank: the absorbance throughout this range does not exceed 0.2 (distinction from *benzene*,

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* Patent pending. See notice, page ii.

toluene, p-toluenesulfonic acid or its esters).

Nonvolatile residue—Allow 10 ml. of Flurothyl to evaporate at room temperature in a tared evaporating dish, and dry the residue at 50° for 2 hours: the weight of the residue does not exceed 2 mg.

Peroxide—Place 10 ml. of Flurothyl in a glass-stoppered, 25-ml. cylinder containing 1 ml. of a freshly prepared solution of potassium iodide (1 in 10), and shake occasionally during 1 hour, protecting the mixture from light. View the mixture transversely against a white background: no color is seen in either liquid.

Assay—Inject 30 µl. of Flurothyl into a suitable gas chromatograph, page 787, equipped with a thermal conductivity detector. Under typical conditions, the instrument contains a 3-m. × 6-mm. (outside diameter) column packed with diethylene glycol succinate 20 percent, on calcined diatomaceous silica (Chromosorb P); the column is maintained at a temperature of 70°, the injection port is maintained at 150°, the detector block is maintained at 100–150°, and helium is used as a carrier gas at a flow rate of about 80 ml. per minute. From the area under the curve, calculate the percent (a/a) of $C_4H_4F_6O$ in the Flurothyl taken.

Packaging and storage—Preserve Flurothyl in single-dose glass ampuls, and avoid exposure to excessive heat.

Category—Central stimulant (convulsant).

Application—**1 ml.** by special inhalation.

Fluroxene*

$CF_3CH_2—O—CH{=}CH_2$

2,2,2-Trifluoroethyl Vinyl Ether

$C_4H_5F_3O$ Mol. wt. 126.08

Fluroxene contains not less than 99.0 percent and not more than 100.0 percent of $C_4H_5F_3O$. It contains a suitable stabilizer.

Caution—Fluroxene is highly volatile and flammable. Its vapor, when mixed with air and ignited, may explode.

Description—Fluroxene is a clear, practically colorless, volatile liquid having a mild, ethereal odor. It boils at about 43°.

Solubility—Fluroxene is slightly soluble in water. It is miscible with alcohol, with ether, with acetone, and with most halogenated solvents.

Specific gravity, page 866—The specific gravity of Fluroxene is not less than 1.125 and not more than 1.129.

Refractive index, page 858—The refractive index of Fluroxene is not less than 1.319 and not more than 1.320 at 20°.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 20 solution of Fluroxene in carbon disulfide exhibits maxima at the following wavelengths, in µ: 3.45 (*w*), 6.13 (*m*), 6.22 (*m*), 7.88 (*s*), 8.35 (*s*), 8.63 (*s*), 8.80 (*m*), 9.10 (w), 9.69 (*w*), 10.27 (*m*), 10.40 (*m*), 10.76 (*w*), 11.75 (*w*), 12.12 (*m*), and 14.83 (*w*).

Reaction—Agitate 5 ml. of Fluroxene with 2 ml. of carbon dioxide-free water for 30 seconds: the water layer is neutral to litmus.

Nonvolatile residue—Allow 10 ml. of Fluroxene to evaporate at room temperature in a tared evaporating dish, and dry the residue at 50° for 2 hours: the weight of the residue does not exceed 2 mg.

Foreign odor—Place 10 ml. of Fluroxene in a small, dry evaporating dish, and allow to evaporate spontaneously to about 1 ml.: no foreign odor is perceptible during the evaporation. Pour the residue onto odorless filter paper: no foreign odor is perceptible as the last portion disappears from the paper.

Aldehydes—Place 20 ml. of Fluroxene in a glass-stoppered cylinder, add 7 ml. of a mixture of 1 ml. of alkaline mercuric-potassium iodide T.S. and 17 ml. of a saturated solution of sodium chloride. Stopper the cylinder, shake it vigorously for 10 seconds, and then set aside for 1 minute: the water layer shows no turbidity.

Assay—Inject 30 µl. of Fluroxene into a suitable gas chromatograph, page 787. Under typical conditions the instrument contains a 3 m. × 6-mm. (outside diameter) column packed with di(2-ethylhexyl)-sebacate, 20 percent on purified siliceous earth; the column is heated initially at 50° and after 5 minutes is increased at a rate of 10° per minute to 100°. The column is maintained at 100° for 8 minutes; the injection port is maintained at 150°, and helium is used as the carrier gas at a flow rate of about 80 ml. per minute. From the area under the curve, calculate the percent (a/a) of $C_4H_5F_3O$ in the Fluroxene taken.

Packaging and storage—Preserve Fluroxene in tight, light-resistant containers, and avoid exposure to excessive heat.

Category—General anesthetic.

Usual dose—By inhalation as required.

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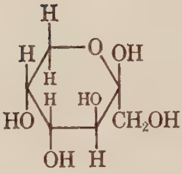
* Patented. See notice, page ii.

Fructose



D(−)-Fructose

$C_6H_{12}O_6$ Mol. wt. 180.16

Fructose, dried in vacuum at 70° for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_6H_{12}O_6$.

Description—Fructose occurs as colorless crystals or as a white, crystalline or granular powder. It is odorless and has a sweet taste.

Solubility—Fructose is soluble in alcohol and in methanol. It is freely soluble in water.

Identification—

A: To 5 ml. of hot alkaline cupric tartrate T.S. add a few drops of a solution of Fructose (1 in 10): a copious red precipitate of cuprous oxide is formed.

B: Heat to about 60°, a mixture of 1 g. of phenylhydrazine hydrochloride and 1.5 g. of sodium acetate with 10 ml. of water, cool, and filter. To 5 ml. of this solution in a test tube add 1.5 ml. of a solution of Fructose (1 in 10), heat in boiling water for 5 minutes, then cool, filter, and wash the precipitate with three 10-ml. portions of water followed by single washings of 5 ml. each of alcohol and of ether. Dry the residue at 105° for 30 minutes: the yellow osazone so obtained melts between 205° and 210° (with decomposition), page 814.

Color of solution—Dissolve 25 g. of Fructose in sufficient water to make 50.0 ml. of solution: the solution has no more color than a solution prepared by mixing 1.0 ml. of cobaltous chloride C.S., 3.0 ml. of ferric chloride C.S., and 2.0 ml. of cupric sulfate C.S. with water to make 10 ml., and diluting 3 ml. of this solution with water to make 50 ml. Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface.

Acidity—Dissolve 5 g. of Fructose in 50 ml. of carbon dioxide-free water. Add 3 drops of phenolphthalein T.S., and titrate with 0.02 *N* sodium hydroxide to the production of a distinct pink color: not more than 0.5 ml. of 0.02 *N* sodium hydroxide is required for neutralization.

Loss on drying, page 814—Dry Fructose in vacuum at 70° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Fructose yields not more than 0.5 percent of residue on ignition.

Chloride, page 784—A 2-g. portion of Fructose shows no more chloride than corresponds to 0.5 ml. of 0.02 *N* hydrochloric acid (0.018 percent).

Sulfate, page 784—A 2-g. portion of Fructose shows no more sulfate than corresponds to 0.5 ml. of 0.02 *N* sulfuric acid (0.025 percent).

Arsenic—A *Test Preparation* prepared with 10.0 g. of Fructose, as directed for organic compounds, meets the requirements of the *Arsenic Test,* page 777 (1 part per million As).

Calcium—To 10 ml. of Fructose solution (1 in 10) add 1 ml. of ammonium oxalate T.S.: the solution remains clear for 1 minute.

Heavy metals, page 806—Dissolve 5 g. of Fructose in 23 ml. of water, and add 2 ml. of diluted acetic acid: the heavy metals limit for Fructose is 5 parts per million.

Hydroxymethylfurfural—Transfer to a test tube 10 ml. of a solution of Fructose (1 in 10), add 5 ml. of ether, and shake vigorously. Transfer 2 ml. of the ether layer to a test tube and add 1 ml. of a solution of resorcinol in hydrochloric acid (1 in 100): a slight pink color may form, but no cherry-red color appears immediately.

Assay—Transfer about 10 g. of Fructose, previously dried in vacuum at 70° for 4 hours and accurately weighed, to a 100-ml. volumetric flask, and dissolve in 50 ml. of water. Add 0.2 ml. of ammonia T.S., then dilute to volume with water, and mix. After 30 minutes, determine the angular rotation in a 100-mm. tube at 25° (see page 822). The observed rotation, in degrees, multiplied by 1.124, represents the weight, in g., of $C_6H_{12}O_6$ in the Fructose taken.

Packaging and storage—Preserve Fructose in well-closed containers.

CATEGORY and DOSE—See Fructose Injection and Fructose and Sodium Chloride Injection.

Fructose Injection

Fructose Injection is a sterile solution of fructose in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{12}O_6$.

Bacteriostatic agents are not to be added to Fructose Injection.

Identification—Fructose Injection responds to the *Identification tests* under *Fructose*, page 320.

Pyrogen—Fructose Injection, diluted if necessary with water for injection to contain 10 percent of fructose, meets the requirements of the *Pyrogen Test*, page 851.

pH, page 824—The pH of Fructose Injection is between 3.0 and 6.0.

Heavy metals—Place a volume of Fructose Injection, equivalent to 3 g. of fructose, in a porcelain dish and evaporate to a volume of about 10 ml. Cool, dilute to 20 ml. with water, add 2 ml. of diluted acetic acid, and add water to make 25 ml.: the heavy metals limit for Fructose Injection is 5 parts per million.

Hydroxymethylfurfural—Fructose Injection meets the requirements of the test for *Hydroxymethylfurfural* under *Fructose*, page 320.

Other requirements—Fructose Injection meets the requirements under *Injections*, page 810.

Assay—Transfer an accurately measured volume of Fructose Injection, containing about 5 g. of fructose, to a 100-ml. volumetric flask. Add 0.2 ml. of ammonia T.S., dilute to volume with water, and mix. After 30 minutes determine the angular rotation in a 200-mm. tube at 25° (see page 822). The observed rotation, in degrees, multiplied by 0.5618, represents the weight, in g., of $C_6H_{12}O_6$ in the volume of the Injection taken for the assay.

Packaging and storage—Preserve Fructose Injection in single-dose containers, preferably of Type I or Type II glass.

Injection available—Fructose Injection usually available contains the following amount of fructose: 100 g. in 1000 ml.

CATEGORY—Fluid and nutrient replenisher.

USUAL DOSE—Intravenous and subcutaneous, as required.

Fructose and Sodium Chloride Injection

Fructose and Sodium Chloride Injection is a sterile solution of fructose and sodium chloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amounts of $C_6H_{12}O_6$ (fructose) and of NaCl (sodium chloride).

Bacteriostatic agents are not to be added to Fructose and Sodium Chloride Injection.

Identification—Fructose and Sodium Chloride Injection responds to the *Identification tests* under *Fructose*, page 320, and to the tests for *Sodium*, page 810, and for *Chloride*, page 808.

Pyrogen—Fructose and Sodium Chloride Injection, diluted, if necessary, with water for injection to contain not more than 0.9 percent of sodium chloride and not more than 10 percent of fructose, meets the requirements of the *Pyrogen Test*, page 851.

pH, page 824—The pH of Fructose and Sodium Chloride Injection is between 3.0 and 6.0.

Heavy metals, page 806—Proceed as directed in the *Heavy metals test* under *Fructose Injection*, page 321: the heavy metals limit for Fructose and Sodium Chloride Injection is 5 parts per million.

Hydroxymethylfurfural—Fructose and Sodium Chloride Injection meets the requirements of the test for *Hydroxymethylfurfural* under *Fructose*, page 320.

Other requirements—Fructose and Sodium Chloride Injection meets the requirements under *Injections*, page 810.

Assay for fructose—Transfer an accurately measured volume of Fructose and Sodium Chloride Injection, containing about 5 g. of fructose, to a 100-ml. volumetric flask. Add 0.2 ml. of ammonia T.S., dilute to volume with water, and mix. After 30 minutes determine the angular rotation in a 200-mm. tube at 25° (see page 822). The observed rotation in degrees, multiplied by 0.5618, represents the weight, in g., of $C_6H_{12}O_6$ in the volume of the Injection taken for the assay.

Assay for sodium chloride—Transfer an accurately measured volume of Fructose and Sodium Chloride Injection, equivalent to about 200 mg. of sodium chloride, to a glass-stoppered flask, and add water, if necessary, to make about 50 ml. Add, while agitating, 50.0 ml. of 0.1 *N* silver nitrate, then add 3 ml. of nitric acid and 5 ml. of nitrobenzene, and shake well. Add 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 5.844 mg. of NaCl.

Packaging and storage—Preserve Fructose and Sodium Chloride Injection in single-dose containers, preferably of Type I or Type II glass.

Injection available—Fructose and Sodium Chloride Injection usually available contains the following amounts of fructose and sodium chloride: fructose, 100 g., and sodium chloride, 9 g. in 1000 ml.

Category—Fluid, nutrient, and electrolyte replenisher.

Usual dose—Intravenous and subcutaneous, as required.

Basic Fuchsin

Basic Fuchsin is a mixture of rosaniline and pararosaniline hydrochlorides.

Description—Basic Fuchsin occurs as a dark green powder or greenish glistening crystalline fragments having a bronze-like luster, and not more than a faint odor.

Solubility—Basic Fuchsin is soluble in water, in alcohol, and in amyl alcohol. It is insoluble in ether.

Identification—

A: To 5 ml. of a solution (1 in 1000) of Basic Fuchsin add a few drops of hydrochloric acid: a yellow color is produced (*distinction from acid fuchsin*).

B: To 5 ml. of a solution (1 in 500) of Basic Fuchsin add a few drops of tannic acid T.S.: a red precipitate forms.

C: To 10 ml. of a solution (1 in 500) of Basic Fuchsin add 10 ml. of ammonia T.S. and 500 mg. of zinc dust, and agitate the mixture: the solution becomes decolorized. Place a few drops of the decolorized solution upon filter paper and nearby, on the same paper, place a few drops of diluted hydrochloric acid: a red color develops at the zone of contact.

Loss on drying, page 814—Dry Basic Fuchsin at 105° to constant weight: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Ignite 1 g. of Basic Fuchsin with 0.5 ml. of sulfuric acid: the weight of the residue is not more than 0.3 percent.

Alcohol-insoluble substances—Boil 1 g. of Basic Fuchsin, accurately weighed, with 50 ml. of alcohol under a reflux condenser for 15 minutes, filter through a tared filtering crucible, wash the residue on the filter with hot alcohol until the washings cease to be colored violet, and dry the crucible at 105° for 1 hour: the insoluble residue amounts to not more than 1 percent.

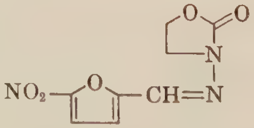
Arsenic—A *Test Preparation* of 1.25 g. of Basic Fuchsin, prepared as directed for organic compounds, meets the requirements of the *Arsenic Test*, page 777 (8 parts per million As).

Lead—Place 1 g. of Basic Fuchsin in a small Kjeldahl flask, add 5 ml. of sulfuric acid, and insert a small funnel into the flask. Gently rotate the flask until the sulfuric acid has completely wetted the Basic Fuchsin, then heat with a small flame until complete carbonization has taken place. Allow to cool, and add, in small quantities, 5 ml. of nitric acid. Again heat gently until fumes of sulfur trioxide are evolved. Allow to cool, add another 5 ml. of nitric acid, and again heat to the evolution of sulfur trioxide. Allow to cool, add about 25 ml. of water, and boil for a few minutes. After cooling, neutralize with stronger ammonia water, using litmus paper as the indicator, and add 5 ml. of nitric acid. Transfer the solution completely to a 100-ml. volumetric flask, dilute to volume, and mix. Use 20 ml. of this solution for the *Lead Limit Test*, page 813. Basic Fuchsin contains not more than 30 parts per million of lead.

Packaging and storage—Preserve Basic Fuchsin in well-closed containers.

Category—Local anti-infective.

Furazolidone*



3-[(5-Nitrofurfurylidene)amino]-2-oxazolidinone

$C_8H_7N_3O_5$ Mol. wt. 225.16

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* Patented. See notice, page ii.

Furazolidone contains not less than 97.0 percent and not more than 103.0 percent of $C_8H_7N_3O_5$, calculated on the dried basis.

Description—Furazolidone occurs as a yellow, odorless, crystalline powder. It is tasteless at first, developing a bitter aftertaste.

Solubility—Furazolidone is practically insoluble in water, in alcohol, and in carbon tetrachloride.

Identification—To about 50 mg. of Furazolidone add 5 ml. of water and 5 ml. of sodium hydroxide T.S.: an orange-red solution is formed.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Furazolidone, previously dried at 100° for 1 hour, exhibits maxima only at the same wavelengths as that of NF Furazolidone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Furazolidone, prepared as directed in the *Assay*, exhibits maxima and minima at the same wavelengths as that of NF Furazolidone Reference Standard, similarly measured.

Loss on drying, page 814—Dry Furazolidone for 1 hour at 100°: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Furazolidone yields not more than 0.05 percent of residue on ignition.

Assay—Transfer about 100 mg. of Furazolidone, accurately weighed, to a 250-ml. volumetric flask, dilute to volume with dimethylformamide, and mix. Transfer 5.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Furazolidone Reference Standard, in the same medium, at a concentration of about 8 mcg. per ml., in 1-cm. cells, at the maximum at about 367 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_8H_7N_3O_5$ in the Furazolidone taken by the formula $12.5C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Furazolidone in tight, light-resistant containers and avoid exposure to direct sunlight.

CATEGORY—Local anti-infective, local antitrichomonal.

Furazolidone and Nifuroxime Powder

Furazolidone and Nifuroxime Powder contains not less than 0.09 percent and not more than 0.11 percent of $C_8H_7N_3O_5$ (furazolidone), and not less than 0.45 percent and not more than 0.55 percent of $C_5H_4N_2O_4$ (nifuroxime) in a suitable, slightly acidified powder base.

Identification—Mix about 250 mg. of Furazolidone and Nifuroxime Powder with 5 ml. of water and add 5 ml. of sodium hydroxide T.S.: an orange-red color develops.

pH, page 824—The pH of a dispersion of Furazolidone and Nifuroxime Powder in carbon dioxide-free water (1 in 25) is between 3.0 and 4.5.

Other tests—Not less than 99 percent of Furazolidone and Nifuroxime Powder passes through a No. 100 sieve (see page 849).

Assay—

Chromatographic column—Prepare a chromatographic column as directed in the *Assay* under *Furazolidone* and *Nifuroxime Suppositories*, page 324.

NOTE: Protect all solutions from light.

Furazolidone standard preparation—Transfer to a 500-ml. volumetric flask about 40 mg. of NF Furazolidone Reference Standard, previously dried at 100° for 1 hour and accurately weighed, dissolve it in 50 ml. of dimethylformamide, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 200-ml. volumetric flask, add 39.5 ml. of dimethylformamide, dilute to volume with water, and mix.

Nifuroxime standard preparation—Transfer to a 500-ml. volumetric flask about 50 mg. of NF Nifuroxime Reference Standard, previously dried at 55° for 2 hours and accurately weighed, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer about 2 g. of Furazolidone and Nifuroxime Powder to a 100-ml. volumetric flask, add 50 ml. of water, agitate for 10 minutes, dilute to volume with water, and mix. Shake thoroughly just prior to use in the *Procedure.*

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Furazolidone and Nifuroxime Suppositories,* page 324, but dilute the nifuroxime eluate to 100.0 ml. rather than to 50.0 ml.

Calculation for nifuroxime—Calculate the quantity, in mg., of $C_5H_4N_2O_4$ in the Powder sample taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Nifuroxime standard preparation.*

Calculation for furazolidone—Calculate the quantity, in mg., of $C_8H_7N_3O_5$ in the Powder sample taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Furazolidone standard preparation.*

Packaging and storage—Preserve Furazolidone and Nifuroxime Powder in tight, light-resistant containers.

Category—Antitrichomonal, local anti-infective.

Application—Vaginal insufflation, one or two times a week.

Furazolidone and Nifuroxime Suppositories

Furazolidone and Nifuroxime Suppositories contain not less than 0.225 percent and not more than 0.275 percent of $C_8H_7N_3O_5$ (furazolidone), and not less than 0.337 percent and not more than 0.413 percent of $C_5H_4N_2O_4$ (nifuroxime).

Identification—Disperse about 500 mg. of Furazolidone and Nifuroxime Suppositories in 5 ml. of water and add 5 ml. of sodium hydroxide T.S.: an orange-red color develops.

Assay—

Chromatographic column—Pack a pledget of fine glass wool at the base of a standard 10 × 150-mm. chromatographic tube. Add to the tube about 63.5 mm. of adsorbent, prepared by thoroughly mixing 1 part of acid-activated montmorillonite and two parts of unwashed and unignited purified siliceous earth, and pack carefully to avoid air pockets or channels. Wash the column so prepared with at least 10 ml. of water and discard the washings.

Note: Protect all solutions from light.

Furazolidone standard preparation—Transfer to a 500-ml. volumetric flask about 50 mg. of NF Furazolidone Reference Standard, previously dried at 100° for 1 hour and accurately weighed, dissolve it in 50 ml. of dimethylformamide, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 200-ml. volumetric flask, add 39.5 ml. of dimethylformamide, dilute to volume with water, and mix.

Nifuroxime standard preparation—Transfer to a 1000-ml. volumetric flask about 75 mg. of NF Nifuroxime Reference Standard, previously dried at 55° for 2 hours and accurately weighed, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a 200-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer to a small beaker about 2 g. of Furazolidone and Nifuroxime Suppositories, accurately weighed, and dissolve in about 30 ml. of warm water (not above 50°). With the aid of water, quantitatively transfer the clear, yellow solution to a 200-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Add 5.0 ml. of the *Assay preparation* to the top of the column, then after almost all of the solution has passed into the column, complete the elution of the nifuroxime with about 40 ml. of water, maintaining the fluid level above the adsorbant column throughout the elution. Gentle vacuum may be applied to provide a flow of about 0.5 ml. per minute from the column. Dilute the nifuroxime eluate to 50.0 ml. with water, mix, centrifuge for 15 minutes, and filter through hard paper. To elute the furazolidone, pass through the column 10.0 ml. of dimethylformamide followed by about 30 ml. of water. Dilute the eluate to 50.0 ml. with water, mix, centrifuge for 15 minutes, and filter through hard paper.

Determine the absorbance of each solution in a 1-cm. cell, with a suitable spectrophotometer, at 341 mμ for the nifuroxime assay solution and at 367 mμ for the furazolidone assay solution, using water as the blank for the nifuroxime and a 1:4 dimethylformamide-water mixture as the blank for the furazolidone. Record the absorbance of each assay solution as A_U and that of the corresponding *Standard preparation* as A_S.

Calculation for nifuroxime—Calculate the quantity, in mg., of $C_5H_4N_2O_4$ in the portion of the Suppositories taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Nifuroxime standard preparation.*

Calculation for furazolidone—Calculate the quantity, in mg., of $C_8H_7N_3O_5$ in the portion of the Suppositories taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Furazolidone standard preparation.*

Packaging and storage—Preserve Furazolidone and Nifuroxime Suppositories in bulk in tight containers at temperatures below 37°. Do not expose unwrapped suppositories to sunlight.

Category—Antitrichomonal; local anti-infective.

Usual dose—Vaginal, one suppository one or two times a day.

Gas Gangrene and Tetanus Antitoxin, page 689

Gitalin

Gitalin is a cardiotonic glycosidal constituent obtained from *Digitalis purpurea* Linné (Fam. *Scrophulariaceæ*). It contains not less than 13.0 percent and not more than 19.0 percent of gitoxin, not less than 13.0 percent and not more than 19.0 percent of gitaloxin, and not less than 14.0 percent and not more than 20.0 percent of digitoxin calculated on the dried basis.

Description—Gitalin occurs as a white or pale buff, amorphous powder. It decomposes with liquefaction between 120° and 150°.

Solubility—Gitalin is freely soluble in acetone, in alcohol, in chloroform, and is very slightly soluble in ether.

Identification—Dissolve 1.2 mg. of Gitalin in 0.5 ml. of a mixture of chloroform and methanol (1:1). Dissolve 1.2 mg. of NF Gitalin Reference Standard in 0.5 ml. of the same medium. On a suitable thin-layer chromatographic plate (page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 10 µl. of each solution. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of cyclohexane, acetone, and glacial acetic acid (49:49:2) until the solvent front has moved about three-fourths of the length of the plate. Dry the plate at 100° to remove the solvent. Spray the plate with a mixture of 1 part sodium *p*-toluenesulfonchloramide solution (3 in 100) and 15 parts alcoholic trichloroacetic acid solution (1 in 4), heat at 115° for 15 minutes, and observe under longwave ultraviolet light: the R_f values and fluorescence of the spots obtained from the sample solution correspond to those obtained from the Reference Standard solution.

Loss on drying, page 814—Dry Gitalin in vacuum over phosphorus pentoxide for 3 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Gitalin yields not more than 0.5 percent of residue on ignition.

Assay—

Reagent—Mix 4 ml. of a freshly prepared 3 in 100 solution of sodium *p*-toluenesulfonchloramide with 60 ml. of a 1 in 4 solution of trichloroacetic acid in alcohol.

Xanthydrol solution—Dissolve 30 mg. of xanthydrol in a mixture of 50 ml. of glacial acetic acid and 3 ml. of hydrochloric acid, dilute to 300 ml. with glacial acetic acid, and mix. Prepare this solution fresh.

Preparation of chromatograms—Cut a 58 × 60-cm. sheet of suitable filter paper* into 14.5 × 60-cm. strips. Fold each strip 6 cm. from the top for suspension on the antisiphon rods. On each of 3 papers draw two 1.5-cm. horizontal spotting lines, 8.5 cm. from the top of the paper and 3 cm. from each side edge of the paper. One of these is for the sample application and the other is for the standard application. Mark the fourth paper with two 1.5-cm. lines, 8.5 cm. from the top and 1.5 cm. and 4.5 cm. from one side edge. These two applications (one sample and one standard) are chromatographed to aid in the location and identification of the 3 major glycosides being analyzed. The other half of this fourth paper is used as a paper blank. Impregnate the four papers with a mixture of formamide and acetone (1:4) contained in a closed vessel. Immerse the papers in this solution for 5 minutes, then remove, drain momentarily in the direction of chromatography (*i.e.*, holding the top of the paper), and quickly blot with filter paper.

Standard preparation—Dissolve about 60 mg. of NF Gitalin Reference Standard, accurately weighed, in 2.0 ml. of a mixture of chloroform-methanol (1:1).

Assay preparation—Dissolve about 60 mg. of Gitalin, accurately weighed, in 2.0 ml. of chloroform-methanol (1:1).

Procedure—Streak 10 µl. of the *Assay preparation* on the sample spotting line on each of the four papers. In the same manner, apply 10 µl. of the *Standard preparation*. Place the four papers in troughs of a suitable chromatographic chamber prepared for descending chromatography (see page 789) without paper liner. Cover the bottom of the chamber with a 3-cm. layer of the mobile phase consisting of xylene-methyl ethyl ketone (1:1), saturated with formamide. Place the mobile phase in the troughs containing the chromatograms, and allow to run for 4.5 hours or about 1 hour longer than it takes for the solvent front to reach the bottom of the chromatogram. Remove the chromatograms, and place in a draft oven for 1 hour at 100°, to remove the formamide. Place the fourth paper (the chromatogram containing the sample, standard, and blank areas) flat on a glass plate. Using a micropipet or a pointed porous nylon applicator, apply three parallel streaks of the *Reagent* to the sample and the standard areas, one streak through the midpoint of the origin line and one through each end of this line, from the spotting line to the lower edge of the paper. Make these streaks as narrow as possible, approaching a pencil-line in thickness.

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* Schleicher and Schuell filter paper no. 2043B, or equivalent, is suitable.

Heat the paper at 110° to 120° for 3 minutes, then view under longwave ultraviolet light, and mark the fluorescent lines carefully with a pencil. Cut away the half of the paper which is to be used for a blank, and keep for marking when the size of the band areas to be analyzed is determined. Spray the other half of the paper, which has been streaked and marked, with the *Reagent*, and heat for 3 minutes at 110° to 120°. View under longwave ultraviolet light: the bands of gitoxin (and the less polar band containing mono- and bis-gitoxin), gitaloxin (and the less polar band containing mono- and bis-gitaloxin), and digitoxin (and the less polar band containing mono- and bis-digitoxin) are visible through fluorescence; outline these bands carefully.

[NOTE: Gitoxin has blue fluorescence and is the slowest moving of the three strongest bands. Gitaloxin has blue fluorescence and is the middle one of the three strongest bands. Digitoxin has yellow fluorescence and is the fastest moving of the three strongest bands. Minor glycosides, strospeside, verodoxin, gitoxigenin, and digitoxigenin are detectable but are not included for quantitation.]

Streak each sample and standard of the three papers to be analyzed with the *Reagent*, applying it in three narrow, parallel lines using the same technique as was used for the fourth paper. Heat, and mark under longwave ultraviolet light, using the sprayed fourth paper as a reference for estimating the width of the bands.

When the average area for each of the three glycosides is known, mark the blank paper accordingly. Evaluate each glycoside (including its mono- and bis-compounds) and its corresponding blank separately: cut each into 1-cm. squares, and place into a properly labeled 25 × 200-mm. tube with plastic-lined screw cap.

Spray the remaining paper of each cut chromatogram with the *Reagent*, and heat to determine if any of a desired band was missed in cutting. If more than a trace of a desired band is detectable, discard the corresponding band and base the result on the average of the two chromatograms which were cut satisfactorily.

Transfer 10.0 ml. of *Xanthydrol solution* into each glycoside tube and into a blank tube. Tighten the screw cap, and agitate each tube for about 10 seconds. Heat the tubes in a boiling water bath for 3 minutes, and then allow to stand in a room-temperature water bath protected from light until the absorbance is read. (The xanthydrol colors are stable for several hours if protected from light exposure.) Determine the absorbance of each solution, at the maximum at about 531 mμ, with a suitable spectrophotometer using alcohol to set the instrument. Subtract the appropriate paper blank absorbance from each glycoside absorbance, and calculate the percent of glycoside in the sample by comparison with the average corrected absorbance for the corresponding standard glycoside of known concentration, using the following formula: % glycoside = $(A_U/A_S) \times (W_S/W_U) \times$ (% glycoside in Standard), in which A_U is the absorbance of the glycoside sample, A_S is the absorbance of the respective glycoside standard, W_U is the weight of the sample taken, in mg., and W_S is the weight of the NF Gitalin Reference Standard, in mg., used in preparing the *Standard preparation*.

Packaging and storage—Preserve Gitalin in tight, light-resistant containers.

CATEGORY—Cardiotonic.

USUAL DOSE—Initial—rapid digitalization, **2.5 mg.** followed by **750 mcg.** every 6 hours until therapeutic effect or toxicity develops, with a total dose of about **6 mg.** being given in 24 hours; slow digitalization, **1.5 mg.** daily for 4 to 6 days. Maintenance, **0.5 mg.** daily.

USUAL DOSE RANGE—Maintenance, **250 mcg.** to **1.25 mg.** daily.

Gitalin Tablets

Gitalin Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of gitalin.

Identification—Evaporate the remaining 20 ml. of chloroform extract, obtained in the *Assay*, to dryness on a steam bath, dissolve the residue in 0.5 ml. of a mixture of chloroform and methanol (1:1), and proceed as directed in the *Identification test* under *Gitalin*, page 325, beginning with "Dissolve 1.2 mg. of NF Gitalin Reference Standard. . . . "

Disintegration, page 878—The disintegration time limit for Gitalin Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Gitalin Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Trinitrophenol solution—On the day of use, dissolve 2.0 g. of trinitrophenol in 50 ml. of methanol, add 10 ml. of water, then add 5 ml. of sodium hydroxide solution (1 in 10) and sufficient water to make 100 ml. Mix, and allow to stand in the dark for at least 30 minutes before use. If the solution is not clear, filter before use.

Standard preparation—Dissolve about 50 mg. of NF Gitalin Reference Standard, accurately weighed, in sufficient methanol to make 50.0 ml., and mix. Transfer 3.0 ml. of this solution to a 60-ml. separator, and continue as directed under *Assay preparation*, beginning with "... add 10 ml. of water, and mix."

Assay preparation—Weigh and finely powder not less than 20 Gitalin Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 3 mg. of gitalin, to a 60-ml. separator containing 3 ml. of methanol, add 10 ml. of water, and mix. Add 15 ml. of chloroform, and shake for 2 minutes. Filter the separated chloroform layer through a chloroform-moistened pledget of cotton into a 50-ml. volumetric flask, and repeat the extraction procedure with two additional 15-ml. portions of chloroform. Dilute to volume with chloroform, and mix.

Procedure—Transfer 15.0 ml. each of the *Standard preparation* and of the *Assay preparation* to low-actinic 50-ml. flasks, and evaporate to dryness on a steam bath with the aid of a stream of nitrogen. Pipet 10.0 ml. of methanol into each flask, swirl to dissolve the residue, and pipet 10.0 ml. of methanol into a third flask to serve as the blank. Pipet 10.0 ml. of *Trinitrophenol solution* into each flask, mix, and allow to stand for 60 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at 495 mμ, with a suitable spectrophotometer, using methanol as the blank, and correct the absorbance of each solution by subtracting the absorbance of the reagent blank. The spectrophotometric readings must be taken without delay since heat from the light source causes error. Record the corrected absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of gitalin in the portion of Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

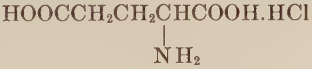
Packaging and storage—Preserve Gitalin Tablets in tight containers.

Tablets available—Gitalin Tablets usually available contain the following amount of gitalin: 500 mcg.

CATEGORY and DOSE—See Gitalin.

Gluconate, Potassium, page 572
Gluconate, Potassium, Elixir, page 573
Gluconate, Potassium, Tablets, page 573

Glutamic Acid Hydrochloride



$$\mathrm{HOOCCH_2CH_2\underset{\substack{|\\ NH_2}}{C}HCOOH.HCl}$$

$C_5H_9NO_4.HCl$ Mol. wt. 183.59

Glutamic Acid Hydrochloride, dried at 80° for 4 hours, contains not less than 99.0 percent and not more than 101.0 percent of $C_5H_9NO_4.HCl$.

Description—Glutamic Acid Hydrochloride occurs as a white, crystalline powder. Its solution is acid to litmus.

Solubility—Glutamic Acid Hydrochloride is freely soluble in water. It is almost insoluble in alcohol and in ether.

Identification—

A: To 1 ml. of a solution of Glutamic Acid Hydrochloride (1 in 3) add 1 ml. of barium hydroxide solution (1 in 50), filter, and add 10 ml. of alcohol: a white, crystalline precipitate of barium glutamate forms on standing.

B: Dissolve 25 mg. of Glutamic Acid Hydrochloride in 100 ml. of water. To 1 ml. of this solution add 1 ml. of ninhydrin T.S. and 100 mg. of sodium acetate, and heat in a steam bath for 5 minutes: a violet-blue color is produced.

C: A solution of Glutamic Acid Hydrochloride (1 in 20) responds to the tests for *Chloride*, page 808.

Specific rotation, page 822—The specific rotation of Glutamic Acid Hydrochloride, previously dried at 80° for 4 hours, determined in 3.0 N hydrochloric acid solution containing 125 mg. of Glutamic Acid Hydrochloride in each ml., is between +23.5° and +25.5°.

Loss on drying, page 814—Dry Glutamic Acid Hydrochloride at 80° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Glutamic Acid Hydrochloride yields not more than 0.25 percent residue on ignition.

Readily carbonizable substances, page 856—Dissolve 500 mg. of Glutamic Acid Hydrochloride in 5 ml. of sulfuric acid T.S.: the solution is colorless.

Chloride—Weigh accurately about 325 mg. of Glutamic Acid Hydrochloride, previously dried in vacuum at 80° for 4 hours, and transfer it to a 125-ml. conical flask. Add 25 ml. of water, 10 ml. of glacial acetic acid, and 0.2 ml. of a 1 in 100 solution of eosin in methanol, and titrate with 0.1 *N* silver nitrate to a rose end-point. Each ml. of 0.1 *N* silver nitrate is equivalent to 3.545 mg. of Cl. Not less than 18.8 percent and not more than 19.8 percent of Cl is found.

Sulfate, page 784—To 10 ml. of a solution of Glutamic Acid Hydrochloride (1 in 10), add 3 drops of diluted hydrochloric acid and 5 drops of barium chloride T.S.: the turbidity does not exceed that produced by 1 ml. of 0.02 *N* sulfuric acid (0.1 percent).

Heavy metals, page 806—Dissolve 1 g. of Glutamic Acid Hydrochloride in 15 ml. of water, add 1 ml. of diluted hydrochloric acid, and dilute to 25 ml. with water: the heavy metals limit for Glutamic Acid Hydrochloride is 20 parts per million.

Assay—Dissolve about 300 mg. of Glutamic Acid Hydrochloride, previously dried at 80° for 4 hours and accurately weighed, in 50 ml. of water. Add bromothymol blue T.S., and titrate with 0.1 *N* sodium hydroxide. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 9.180 mg. of $C_5H_9NO_4.HCl$.

Packaging and storage—Preserve Glutamic Acid Hydrochloride in well-closed, light-resistant containers.

CATEGORY—Acidifier (gastric).

USUAL DOSE RANGE—**600 mg.** to **1.8 g.** during meals.

Glutamic Acid Hydrochloride Capsules

Glutamic Acid Hydrochloride Capsules contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_5H_9NO_4.HCl$.

Identification—Macerate the contents of a convenient number of Glutamic Acid Hydrochloride Capsules with sufficient water to make about 5 ml. of a solution (1 in 3). The solution responds to the *Identification tests* under *Glutamic Acid Hydrochloride*, page 327.

Weight variation, page 901—Glutamic Acid Hydrochloride Capsules meet the requirements of the weight variation test for capsules.

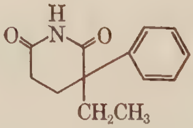
Assay—Transfer, as completely as possible, the contents of not less than 20 Glutamic Acid Hydrochloride Capsules into a 1000-ml. volumetric flask. Wash the emptied capsules with cold water and transfer the washings to the flask. Add water to volume, and shake until the glutamic acid hydrochloride is dissolved. Transfer a convenient volume of the solution, equivalent to about 300 mg. of glutamic acid hydrochloride, to a 300-ml. conical flask, add bromothymol blue T.S., and titrate with 0.1 *N* sodium hydroxide. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 9.180 mg. of $C_5H_9NO_4.HCl$.

Packaging and storage—Preserve Glutamic Acid Hydrochloride Capsules in well-closed containers.

Capsules available—Glutamic Acid Hydrochloride Capsules usually available contain the following amount of glutamic acid hydrochloride: 300 mg.

CATEGORY and DOSE—See Glutamic Acid Hydrochloride.

Glutethimide*



2-Ethyl-2-phenylglutarimide

$C_{13}H_{15}NO_2$ Mol. wt. 217.27

Glutethimide, dried at 45° over phosphorus pentoxide to constant weight, contains not less than 98.0 percent and not more than 101.0 percent of $C_{13}H_{15}NO_2$.

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* Patented. See notice, page ii.

Description—Glutethimide occurs as a white, crystalline powder. A saturated solution of Glutethimide is acid to litmus.

Solubility—Glutethimide is freely soluble in ethyl acetate, in acetone, in ether, and in chloroform. It is soluble in alcohol and in methanol and is practically insoluble in water.

Identification—Dissolve about 500 mg. of Glutethimide in 20 ml. of sodium hydroxide T.S., heat on a steam bath for 30 minutes, cool, and add diluted hydrochloric acid until the mixture is distinctly acid. Collect the precipitate on a filter, wash well with water, and dry at 105° for 1 hour: the 4-phenyl-4-ethylglutaramic acid so obtained melts between 155° and 160°, page 814.

Melting range, page 814—Glutethimide melts between 86° and 89°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Glutethimide, previously dried at 45° over phosphorus pentoxide to constant weight, exhibits maxima only at the same wavelengths as that of NF Glutethimide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 4000 solution of Glutethimide in methanol exhibits maxima and minima at the same wavelengths as that of NF Glutethimide Reference Standard, similarly measured.

Loss on drying, page 814—Dry Glutethimide at 45° over phosphorus pentoxide to constant weight: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Glutethimide yields not more than 0.075 percent of residue on ignition.

Assay—Transfer to a 200-ml. volumetric flask about 50 mg. of Glutethimide, previously dried to constant weight at 45° over phosphorus pentoxide and accurately weighed, add 100 ml. of methanol, shake, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Glutethimide Reference Standard, in the same medium, at a concentration of about 250 mcg. per ml. in 1-cm. cells, at the maximum at about 257 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{13}H_{15}NO_2$ in the Glutethimide taken by the formula $0.2C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Glutethimide in well-closed containers.

CATEGORY—Sedative.

USUAL DOSE RANGE—Sedative, **125** to **250 mg.** up to three times a day; hypnotic, **500 mg.** to **1 g.**

Glutethimide Tablets

Glutethimide Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{15}NO_2$.

Identification—Extract a quantity of finely powdered Glutethimide Tablets, equivalent to about 500 mg. of glutethimide, with three 25-ml. portions of ether. Filter the combined ether extracts and evaporate to dryness without heat: the residue so obtained responds to the *Identification test* under Glutethimide, page 328.

Infrared absorption, page 866—Evaporate to dryness a portion of the eluate obtained in the *Assay.* The infrared absorption spectrum of a potassium bromide dispersion of the residue exhibits absorption maxima only at the same wavelengths as that of NF Glutethimide Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Glutethimide Tablets is 30 minutes.

Weight variation, page 901—Glutethimide Tablets meet the requirements of the weight variation test for tablets.

Assay—

Preparation of chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 200-mm. test tube to which is fused a 5-cm. length of 6 or 8-mm. tubing) with the aid of a tamping rod of stainless steel, aluminum or glass at least 30 cm. long and having a disk with a diameter about 1 mm. less than that of the chromatographic tube. To 2.0 g. of purified siliceous earth in a 100-ml. beaker add 2.0 ml. of 4 N sulfuric acid, and incorporate by kneading thoroughly with a flexible spatula blade until the mixture is fluffy. Transfer to the chromatographic tube and tamp gently to compress the material to a uniform mass. In like manner, mix 2.0 g. of purified siliceous earth with 2.0 ml. of 1 N sodium bicarbonate, transfer it to the chromatographic tube and gently compress with the tamping rod. Wash the column with 50 ml. of water-saturated ether followed by 25 ml. of water-saturated chloroform.

Procedure—Weigh and finely powder not less than 20 Glutethimide Tablets. Transfer to a 100-ml. volumetric flask an accurately weighed portion of the powder, equivalent to about 250 mg. of glutethimide, dilute to volume with water-saturated chloroform, and mix. Transfer 10.0 ml. of this solution to the column and elute with 90 ml. of water-saturated chloroform, collecting the eluate in a 100-ml. volumetric flask. Dilute to volume with water-saturated chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Glutethimide Reference Standard, in the same medium, at a concentration of about 250 mcg. per ml., in 1-cm. cells, at the maximum at about 257 mμ, with a suitable spectrophotometer, using water-saturated chloroform as the blank. Calculate the quantity, in mg., of $C_{13}H_{15}NO_2$ in the portion of the Tablets taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Glutethimide Tablets in well-closed containers.

Tablets available—Glutethimide Tablets usually available contain the following amounts of glutethimide: 125, 250, and 500 mg.

CATEGORY and DOSE—See Glutethimide.

Glycerin Suppositories

Glycerin	**91 g.**
Sodium Stearate	**9 g.**
Purified Water	**5 g.**
To make about	**100 g.**

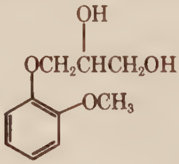
Heat the glycerin in a suitable container to about 120°. Dissolve the sodium stearate, with gentle stirring, in the heated glycerin. Then add the purified water, mix, and immediately pour the hot mixture into a suitable mold, which, if made of metal, previously has been heated and is used while hot. Cool the suppositories completely before removal.

NOTE: If preferred, the sodium stearate for Glycerin Suppositories may be prepared during the making of the Suppositories by the direct reaction between stearic acid and sodium bicarbonate, sodium carbonate, or sodium hydroxide, these being taken in correct proportion.

Packaging and storage—Preserve Glycerin Suppositories in tight containers, preferably at a temperature not above 25°.

CATEGORY—Cathartic.

Glyceryl Guaiacolate



3-(*o*-Methoxyphenoxy)-1,2-propanediol

$C_{10}H_{14}O_4$ Mol. wt. 198.22

Glyceryl Guaiacolate contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{14}O_4$, calculated on the dried basis.

Description—Glyceryl Guaiacolate occurs as a white to slightly gray, crystalline powder having a bitter taste. It may have a slight characteristic odor.

Solubility—Glyceryl Guaiacolate is soluble in water, in alcohol, in chloroform, in glycerin, and in propylene glycol.

Identification—Mix about 5 mg. of Glyceryl Guaiacolate with 1 drop of formaldehyde and a few drops of sulfuric acid: a deep cherry-red to purple color is produced.

Melting range, *Class Ia,* page 815—Glyceryl Guaiacolate melts within a range of 3° between 78° and 82°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Glyceryl Guaiacolate, previously dried in vacuum at 60° to constant weight, exhibits maxima and minima at the same wavelengths as that of NF Glyceryl Guaiacolate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The

ultraviolet absorption spectrum of a 1 in 50,000 solution of Glyceryl Guaiacolate in chloroform exhibits maxima and minima at the same wavelengths as that of NF Glyceryl Guaiacolate Reference Standard, similarly measured.

pH, page 824—The pH of a solution of Glyceryl Guaiacolate (1 in 100) is between 5.0 and 7.0.

Loss on drying, page 814—Dry Glyceryl Guaiacolate in vacuum at 60° to constant weight: it loses not more than 0.5 percent of its weight.

Heavy metals, *Method II,* page 806—The heavy metals limit for Glyceryl Guaiacolate is 25 parts per million.

Free guaiacol—Transfer 1.000 g. of Glyceryl Guaiacolate to a 100-ml. volumetric flask, add 25.0 ml. of water, warming if necessary to effect solution, and 1.0 ml. of potassium ferricyanide T.S., and swirl to moisten the sample. Add 5 ml. of 4-aminoantipyrine solution (1 in 200), and begin timing the reaction with a stop watch. Swirl the flask for 5 seconds, immediately dilute to volume with 0.01 *M* sodium bicarbonate, and mix. Exactly 15 minutes after the addition of the 4-aminoantipyrine solution, determine the absorbance of the solution in a 1-cm. cell, at the maximum at about 500 mμ, with a suitable spectrophotometer, using a reagent blank to set the instrument at zero. The absorbance of the solution is not greater than that of a control similarly prepared with 3.0 ml. of a 1 in 10,000 solution of NF Guaiacol Reference Standard, using the same quantities of the same reagents and in the same manner (0.03 percent).

Assay—Transfer about 100 mg. of Glyceryl Guaiacolate, accurately weighed, to a 100-ml. volumetric flask, add chloroform to volume, and mix. Transfer 4.0 ml. of the solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Glyceryl Guaiacolate Reference Standard, in the same medium at a concentration of about 40 mcg. per ml., in 1-cm. cells, at the maximum at about 276 mμ, with a suitable spectrophotometer, using chloroform as the blank and setting the instrument at zero at 300 mμ. Calculate the quantity, in mg., of $C_{10}H_{14}O_4$ in the Glyceryl Guaiacolate taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Glyceryl Guaiacolate in tight containers.

CATEGORY—Expectorant.

USUAL DOSE—**100 mg.** every 3 or 4 hours.

Glyceryl Guaiacolate Syrup

Glyceryl Guaiacolate Syrup contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{14}O_4$.

Identification—The solution of Glyceryl Guaiacolate prepared for measurement of absorbance in the *Assay* exhibits a maximum at 276 ± 2 mμ.

pH, page 824—The pH of Glyceryl Guaiacolate Syrup is between 2.3 and 3.0.

Assay—Transfer an accurately measured volume of Glyceryl Guaiacolate Syrup, equivalent to about 100 mg. of glyceryl guaiacolate, to a separator, add 5 ml. of diluted sulfuric acid, and extract with four 25-ml. portions of chloroform. Wash the combined chloroform extracts in a second separator with 5 ml. of water, discard the washing, and filter the extracts through chloroform-moistened paper into a 100-ml. volumetric flask. Dilute to volume with chloroform, and mix. Transfer 4.0 ml. of the solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Glyceryl Guaiacolate Reference Standard, in chloroform at a concentration of about 40 mcg. per ml., in 1-cm. cells, at the maximum at about 276 mμ, with a suitable spectrophotometer, using chloroform as the blank and setting the instrument at zero at 300 mμ. Calculate the quantity, in mg., of $C_{10}H_{14}O_4$ in each ml. of the Syrup taken by the formula $2.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of Syrup taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Alcohol, page 772—Glyceryl Guaiacolate Syrup contains from 3 to 4 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Glyceryl Guaiacolate Syrup in tight, light-resistant containers.

Syrup available—Glyceryl Guaiacolate Syrup usually available contains the following amount of glyceryl guaiacolate: 100 mg. in 5 ml.

CATEGORY and DOSE—See Glyceryl Guaiacolate.

Glyceryl Monostearate

Description—Glyceryl Monostearate occurs as a white, wax-like solid or as white, wax-like beads or flakes. It has a slight, agreeable, fatty odor and taste. It is affected by light.

Solubility—Glyceryl Monostearate dissolves in hot organic solvents such as alcohol, mineral or fixed oils, benzene, ether, and acetone. It is insoluble in water but it may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent.

Melting range, page 814—Glyceryl Monostearate does not melt below 55°.

Residue on ignition, page 858—Glyceryl Monostearate yields not more than 0.1 percent of residue on ignition.

Acid value, page 804—The acid value of Glyceryl Monostearate is not more than 18.

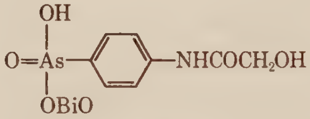
Saponification value, page 805—The saponification value of Glyceryl Monostearate is not less than 155 and not more than 165.

Iodine value, page 804—The iodine value of Glyceryl Monostearate is not more than 6.

Packaging and storage—Preserve Glyceryl Monostearate in tight, light-resistant containers.

CATEGORY—Emulsifying agent.

Glycobiarsol



(Hydrogen *N*-Glycoloylarsanilato)oxobismuth

$C_8H_9AsBiNO_6$ Mol. wt. 499.07

Glycobiarsol contains not less than 97.0 percent and not more than 103.0 percent of $C_8H_9AsBiNO_6$, calculated on the dried basis.

Description—Glycobiarsol occurs as an odorless, yellowish white to flesh-colored, amorphous powder. It decomposes on heating.

Solubility—Glycobiarsol is very slightly soluble in alcohol and in water, and is practically insoluble in benzene, in chloroform, and in ether.

Identification—

A: Dissolve 1 g. of Glycobiarsol in 32 ml. of dilute hydrochloric acid (1 in 15), boil gently for 2 minutes, cool, and divide the solution into three equal portions. To one portion add 1 ml. of sodium sulfide T.S.: a heavy, dark-brown precipitate is formed.

B: To a second portion of the solution prepared in *Identification test A* add bromine T.S. until a permanent, light yellow color is produced and a curdy, white precipitate forms. Separate the precipitate by filtration, dissolve it in 10 ml. of ether, and filter the ether solution. Evaporate the filtrate to dryness, take up the residue in alcohol, add activated charcoal, and filter: the tan-colored crystals of tribromoaniline obtained by crystallization from the alcohol melt between 118° and 121°, page 814.

C: The third portion of the solution prepared in *Identification test A* responds strongly to the *Arsenic Test,* page 777.

Loss on drying, page 814—Dry Glycobiarsol at 105° for 24 hours: it loses not more than 3 percent of its weight.

Arsenic content—Transfer about 300 mg. of Glycobiarsol, previously dried at 105° for 24 hours and accurately weighed, to a 100-ml. Kjeldahl flask. Add 5 ml. of a solution of 1 part of nitric acid in 9 parts of sulfuric acid, and digest over low heat for about 15 minutes or until the mixture is light tan in color. Cool, cautiously dilute with 5 ml. of water, and evaporate until fumes of sulfur trioxide appear. Add 50 mg. of starch, and digest the solution over low heat for about 2 hours or until it becomes light orange in color. Cool, add 50 ml. of water, and transfer the solution to a 600-ml. beaker containing 25 ml. of potassium sodium tartrate solution (1 in 20). Cool the solution with ice, immerse a small piece of congo red paper in it, and add sodium hydroxide solution (4 in 10) until the solution is slightly alkaline. Add diluted sulfuric acid, dropwise, until the solution is slightly acid, neutralize with sodium bicarbonate, and add 3 g. in excess. Titrate the resulting solution with 0.1 *N* iodine. Each ml. of 0.1 *N* iodine is equivalent to 3.746 mg. of As. Not less than 14 percent and not more than 16 percent of As is found.

Free arsanilic acid—

Standard preparation—Place about 500

mg. of arsanilic acid, accurately weighed, in a 1000-ml. volumetric flask, dissolve in sodium hydroxide solution (1 in 1000), dilute to volume with sodium hydroxide solution (1 in 1000), and mix. Pipet 10.0 ml. of this solution into a second 1000-ml. volumetric flask, dilute to volume with sodium hydroxide solution (1 in 1000) and mix.

N-(1-Naphthyl)ethylenediamine dihydrochloride solution—Dissolve 50 mg. of *N*-(1-naphthyl)ethylenediamine dihydrochloride in 15 ml. of water, and dilute with propylene glycol to 50 ml.

Standard arsanilic acid graph—To four 25-ml. volumetric flasks add, respectively, 1.0, 3.0, 5.0, and 7.0-ml. portions of the *Standard preparation*, and for a control add 5 ml. of water to a fifth flask. To each flask add 0.2 ml. of diluted hydrochloric acid and 0.3 ml. of sodium nitrite solution (1 in 50), mix, let stand for 3 to 4 minutes, add 0.3 ml. of sulfamic acid solution (1 in 25), mix, and let stand for 1 minute. Add 1 ml. of *N-(1-Naphthyl)ethylenediamine dihydrochloride solution*, mix, dilute with water to volume, and mix. Determine the absorbance of each solution at 525 mμ with a suitable spectrophotometer, using the control solution as the blank. Plot the observed absorbance on the ordinate scale against the corresponding concentration of arsanilic acid, in mg., on the abscissa scale.

Procedure—Weigh accurately about 150 mg. of Glycobiarsol, and transfer it to a 50-ml. volumetric flask. Add 5 ml. of disodium ethylenediaminetetraacetate solution (1 in 20), and warm the flask, with shaking, at about 90° until solution is complete. Cool to room temperature, dilute with water to volume, and mix. Pipet 10.0 ml. of the solution into a second 50-ml. volumetric flask, dilute with water to volume, and mix. Pipet 5.0 ml. of this solution into a 25-ml. volumetric flask, and to a second 25-ml. volumetric flask add 5 ml. of water to serve as the control. To each flask add 0.2 ml. of diluted hydrochloric acid and 0.3 ml. of sodium nitrite solution (1 in 50), mix, and let stand for 3 to 4 minutes. Add 0.3 ml. of sulfamic acid solution (1 in 25), mix, and let stand for 1 minute. Add 1 ml. of *N-(1-Naphthyl)ethylenediamine dihydrochloride solution*, mix, dilute with water to volume, and mix. Determine the absorbance of the solution at 525 mμ with the same spectrophotometer used in preparing the *Standard arsanilic acid graph*, using the control as the blank. From the observed absorbance calculate the weight of free arsanilic acid in the Glycobiarsol taken. Not more than 1 percent of free arsanilic acid, calculated on the dried basis, is found.

Bismuth content—Transfer about 200 mg. of Glycobiarsol, accurately weighed, to a 250-ml. flask, and add 10.0 ml. of 0.05 *M* disodium ethylenediaminetetraacetate. Warm the flask until the sample is completely dissolved, and cool to room temperature. Add 10 ml. of acetic acid-ammonium acetate buffer T.S., 25 ml. of alcohol, and 2 ml. of dithizone T.S., and titrate the excess disodium ethylenediaminetetraacetate with 0.025 *M* zinc sulfate until the solution is clear rose-pink in color. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate consumed is equivalent to 10.45 mg. of Bi. Glycobiarsol contains not less than 38 percent and not more than 42.5 percent of Bi, calculated on the dried basis.

Assay—Dissolve about 500 mg. of Glycobiarsol, accurately weighed, in 30 ml. of diluted hydrochloric acid, and gently reflux the solution for 5 to 6 minutes. Cool, transfer to a 400-ml. beaker, add 50 g. of crushed ice, and dilute to 200 ml. with water. Titrate slowly with 0.1 *M* sodium nitrite, stirring vigorously, until a sharp-edged blue spot is produced when the titration mixture is spotted on starch iodide paper. When the titration is complete, the end-point is reproducible after the mixture has been allowed to stand for one minute. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 49.91 mg. of $C_8H_9AsBiNO_6$.

Packaging and storage—Preserve Glycobiarsol in well-closed, light-resistant containers.

CATEGORY—Antiamebic.

USUAL DOSE—**500 mg.** three times a day for 7 to 10 days.

Glycobiarsol Tablets

Glycobiarsol Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_9AsBiNO_6$.

Identification—Dissolve a portion of powdered Glycobiarsol Tablets, equivalent to about 1 g. of glycobiarsol, in 32 ml. of dilute hydrochloric acid (1 in 15), boil gently for 2 minutes, cool, and filter: separate 10-ml. portions of this filtrate respond to *Identification tests A* and *C* under *Glycobiarsol*, page 332.

Disintegration, page 878—The disintegration time limit for Glycobiarsol Tablets is 30 minutes.

Weight variation, page 901—Glycobiarsol Tablets meet the requirements of the weight variation test for tablets.

Bismuth content—Weigh and finely powder not less than 20 Glycobiarsol

Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg. of glycobiarsol, to a 250-ml. conical flask, and proceed as directed in the test for *Bismuth content* under *Glycobiarsol*, page 332, beginning with "... add 10.0 ml. of 0.05 *M* disodium ethylenediaminetetraacetate." Glycobiarsol Tablets contain an amount of Bi not less than 38 percent and not more than 42.5 percent of the weight of $C_3H_9AsBiNO_6$ found in the *Assay*.

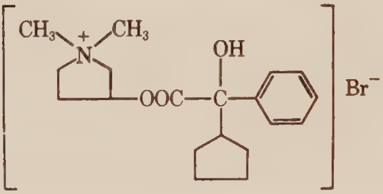
Assay—Transfer an accurately weighed portion of the powder prepared in the test for *Bismuth content*, equivalent to about 500 mg. of glycobiarsol, to a suitable flask, add 30 ml. of diluted hydrochloric acid, and proceed as directed in the *Assay* under *Glycobiarsol*, page 332, beginning with "gently reflux the solution. . . ."

Packaging and storage—Preserve Glycobiarsol Tablets in well-closed, light-resistant containers.

Tablets available—Glycobiarsol Tablets usually available contain the following amount of glycobiarsol: 500 mg.

CATEGORY and DOSE—See Glycobiarsol.

Glycopyrrolate*



3-Hydroxy-1,1-dimethylpyrrolidinium Bromide α-Cyclopentylmandelate

$C_{19}H_{28}BrNO_3$ Mol. wt. 398.34

Glycopyrrolate, dried at 105° for 3 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{19}H_{28}BrNO_3$.

Description—Glycopyrrolate occurs as a white, odorless, crystalline powder.

Solubility—Glycopyrrolate is soluble in water and in alcohol. It is practically insoluble in chloroform and in ether.

Identification—

A: A solution of Glycopyrrolate (1 in 40) responds to the tests for *Bromide*, page 808.

B: Dissolve about 500 mg. of Glycopyrrolate in 20 ml. of water, add 2.5 ml. of sodium hydroxide T.S., and boil for 10 minutes. Cool, add 5 ml. of diluted hydrochloric acid, and filter. Wash the precipitate with five 5-ml. portions of water, and dry the residue at 105° for 1 hour: the crystals of α-phenylcyclopentaneglycolic acid so obtained melt between 146° and 149°, page 814.

Melting range, page 814—Glycopyrrolate melts within a range of 2° between 193° and 198°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Glycopyrrolate, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Glycopyrrolate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2000 solution of Glycopyrrolate in water exhibits maxima and minima at the same wavelengths as that of NF Glycopyrrolate Reference Standard, similarly measured.

Loss on drying, page 814—Dry Glycopyrrolate at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Glycopyrrolate yields not more than 0.3 percent of residue on ignition.

Assay—Dissolve about 800 mg. of Glycopyrrolate, previously dried at 105° for 3 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 39.83 mg. of $C_{19}H_{28}BrNO_3$.

Packaging and storage—Preserve Glycopyrrolate in tight containers.

CATEGORY—Anticholinergic.
USUAL DOSE—**1 mg.** three times a day.
USUAL DOSE RANGE—**1** to **2 mg.**

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* Patented. See notice, page ii.

Glycopyrrolate Tablets

Glycopyrrolate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{19}H_{28}BrNO_3$.

Identification—Blend a portion of finely powdered Glycopyrrolate Tablets, equivalent to about 25 mg. of glycopyrrolate, with 50 ml. of water in a high-speed blender, and filter through very retentive filter paper: the ultraviolet absorption spectrum of the filtrate exhibits maxima and minima at the same wavelengths as that of a 1 in 2000 solution of NF Glycopyrrolate Reference Standard.

Disintegration, page 878—The disintegration time limit for Glycopyrrolate Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Glycopyrrolate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

pH 5.3 Phosphate buffer—Dissolve 38.0 g. of monobasic sodium phosphate and 2.0 g. of anhydrous dibasic sodium phosphate in sufficient water to make 1000.0 ml., and adjust the pH, if necessary, to 5.3 ± 0.1.

Bromocresol purple solution—Dissolve 400 mg. of bromocresol purple in 30 ml. of alcohol, add 6.3 ml. of 0.1 *N* sodium hydroxide, and dilute to 500 ml. with water.

Buffer-dye mixture—On the day of use, mix equal volumes of *pH 5.3 Phosphate buffer* and of *Bromocresol purple solution,* and extract with chloroform until the last extract is colorless.

Standard preparation—Transfer about 100 mg. of NF Glycopyrrolate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Weigh and finely powder not less than 20 Glycopyrrolate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg. of glycopyrrolate, to a 100-ml. volumetric flask, add 50 ml. of water, and shake mechanically for 10 minutes. Dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate. Use the subsequent filtrate as directed in the *Procedure.*

Procedure—Transfer 10.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate separators, each containing 10.0 ml. of *Buffer-dye mixture,* and transfer 10.0 ml. of water to a third separator containing 10.0 ml. of *Buffer-dye mixture* to serve as the blank. Mix, and extract each solution with four 25-ml. portions of chloroform, filtering the extracts from each solution through chloroform-moistened filter paper into separate 100-ml. volumetric flasks. Dilute each solution to volume with chloroform, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 410 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{19}H_{28}BrNO_3$ in the portion of the Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Glycopyrrolate Tablets in tight containers.

Tablets available—Glycopyrrolate Tablets usually available contain the following amounts of glycopyrrolate: 1 and 2 mg.

Category and Dose—See Glycopyrrolate.

Gramicidin

Gramicidin is an antibacterial substance produced by the growth of *Bacillus brevis* Dubos (Fam. *Bacillaceæ*). It may be obtained from tyrothricin.

Gramicidin has a potency of not less than 900 mcg. of activity per mg. Gramicidin conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Gramicidin occurs as a white, or nearly white, odorless, crystalline powder.

Solubility—Gramicidin is soluble in alcohol and insoluble in water.

Color—The absorbance of a 1 in 20 alcohol solution of Gramicidin, determined in a 1-cm. cell, using a suitable spectrophotometer at a wavelength of 440 mμ, does not exceed 0.096.

Packaging and storage—Preserve Gramicidin in tight containers.

Category—Antibacterial.

Application—Topically as 0.05 percent solution.

Gramicidin, Neomycin Sulfate and Polymyxin B Sulfate Ophthalmic Solution, page 475

Green Soap

Green Soap is a potassium soap made by the saponification of suitable vegetable oils, excluding coconut oil and palm kernel oil, without the removal of glycerin.

Green Soap may be prepared as follows:

The Vegetable Oil	380	g.
Oleic Acid	20	g.
Potassium Hydroxide (total alkali 85 percent)	91.7	g.
Glycerin	50	ml.
Purified Water, a sufficient quantity		
To make about	1000	g.

Mix the oil and oleic acid, and heat the mixture to about 80°. Dissolve the potassium hydroxide in a mixture of the glycerin and 100 ml. of purified water, and add the solution, while it is still hot, to the hot oil. Stir the mixture vigorously until emulsified, then heat while continuing the stirring, until the mixture is homogeneous and a test portion will dissolve to give a clear solution in hot water. Add sufficient hot purified water to make the product weigh 1000 g., continuing the stirring until the Soap is homogeneous.

Description—Green Soap occurs as a soft, unctuous, yellowish white to brownish or greenish yellow, transparent to translucent mass. It has a slight, characteristic odor, often suggesting the oil from which it was prepared. Its 1 in 20 solution is alkaline to bromothymol blue T.S.

Water—Place about 5 g. of Green Soap, quickly weighed to the nearest centigram, in the distilling flask of the apparatus for *Moisture Method by Toluene Distillation,* page 886. (The Soap is most conveniently weighed in a boat of metal foil, of a size that will just pass through the neck of the flask.) Place 250 ml. of toluene and 10 g. of anhydrous barium chloride in the flask, connect the flask through a ground-glass joint to the distilling apparatus, fill the receiving tube with toluene, and determine the water as directed, beginning with "Heat the flask gently." The volume of water found corresponds to not more than 52 percent by weight of the Green Soap taken.

Alcohol-insoluble substances—Dissolve about 5 g. of Green Soap, rapidly and accurately weighed, in 100 ml. of hot neutralized alcohol, collect the residue, if any, on a tared filter, thoroughly wash it with hot neutralized alcohol, and dry at 105° for 1 hour: the weight of the residue obtained does not exceed 3 percent of the weight of the Green Soap taken. Save the solution and the residue.

Free alkali hydroxides—To the combined filtrate and washings obtained in the test for *Alcohol-insoluble substances* add 0.5 ml. of phenolphthalein T.S. If a pink color is produced, titrate the solution with 0.1 *N* sulfuric acid until the pink color is just discharged. Each ml. of 0.1 *N* sulfuric acid is equivalent to 5.611 mg. of KOH. The volume of 0.1 *N* sulfuric acid consumed corresponds to not more than 0.25 percent of KOH.

Alkali carbonates—Wash the filter containing the *Alcohol-insoluble substances* with 50 ml. of boiling water, cool, add methyl orange T.S., and titrate the filtrate with 0.1 *N* sulfuric acid. Not more than 0.5 ml. of 0.1 *N* sulfuric acid per g. of Green Soap originally taken is required (0.35 percent as K_2CO_3).

Unsaponified matter—A solution of Green Soap in hot water (1 in 20) is nearly clear.

Characteristics of the liberated fatty acids—Dissolve about 30 g. of Green Soap in 300 ml. of hot water in a beaker, add gradually 60 ml. of diluted sulfuric acid, and heat on a steam bath until the liberated acids form a transparent layer. Decant the fatty acids into a separator, and wash them with 50-ml. portions of hot water until the last washing, when cool, is neutral to methyl orange T.S. Transfer the fatty acids to a dry beaker, and allow them to stand in a warm oven until any water that may be present has separated. Then filter the acids through a dry filter in the warm oven. Determine the acid value (see page 804) of about 1 g., accurately weighed, of the fatty acids: it is not more than 205. Determine the iodine value (see page 804) of 150 to 200 mg., accurately weighed, of the fatty acids: it is not less than 85.

Packaging and storage—Preserve Green Soap in well-closed containers.

Category and Use—See Green Soap Tincture.

Green Soap Tincture

Green Soap	**650 g.**
Lavender Oil	**20 ml.**
Alcohol, a sufficient quantity	
To make	**1000 ml.**

Mix the lavender oil with 300 ml. of alcohol, dissolve in this the green soap by stirring or by agitation, set the solution aside for 24 hours, filter through paper, and add alcohol to make 1000 ml.

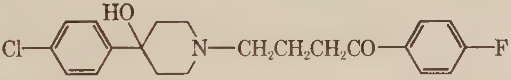
Alcohol content, page 772—Green Soap Tincture contains from 28 to 32 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Green Soap Tincture in tight containers.

Category—Detergent.
For external use—Topically to skin.

Guaiacolsulfonate, Potassium, page 574

Haloperidol*



4-[4-(*p*-Chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone

$C_{21}H_{23}ClFNO_2$ Mol. wt. 375.87

Haloperidol, dried in vacuum at 60° for 3 hours, contains not less than 98.0 percent and not more than 102.0 percent $C_{21}H_{23}ClFNO_2$.

Description—Haloperidol occurs as a white to faintly yellowish, amorphous or microcrystalline powder. Its saturated solution is neutral to litmus.

Solubility—Haloperidol is practically insoluble in water. It is soluble in chloroform, sparingly soluble in alcohol, and slightly soluble in ether.

Melting range, page 814—Haloperidol, dried in vacuum at 60° for 3 hours, melts between 147° and 152°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Haloperidol, previously dried in vacuum at 60° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Haloperidol Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Haloperidol in 0.1 *N* hydrochloric acid–isopropyl alcohol (1:9) exhibits maxima and minima at the same wavelengths as that of NF Haloperidol Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 245 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Haloperidol in vacuum at 60° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Haloperidol yields not more than 0.25 percent of residue on ignition.

Assay—Dissolve about 125 mg. of Haloperidol, previously dried in vacuum at 60° for 3 hours and accurately weighed, in 25 ml. of glacial acetic acid, add 3 drops of α-naphtholbenzein T.S., and titrate with 0.05 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.05 *N* perchloric acid is equivalent to 18.79 mg. of $C_{21}H_{23}ClFNO_2$.

Packaging and storage—Store in tight, light-resistant containers.

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* Patent pending. See notice, page ii.

CATEGORY—Tranquilizer (major).

USUAL DOSE—**1** to **2 mg.** two or three times a day.

USUAL DOSE RANGE—**1** to **5 mg.**; daily doses greater than 15 mg. are not recommended.

Haloperidol Solution

Haloperidol Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{23}ClFNO_2$.

Identification—The solution prepared for measurement of absorbance in the *Assay* exhibits a maximum at 245 ± 2 mμ.

Assay—Transfer an accurately measured volume of Haloperidol Solution, equivalent to about 10 mg. of haloperidol, to a separator, and add 20 ml. of 0.5 *N* hydrochloric acid. Extract the solution with four 20-ml. portions of ether and wash the combined ether extracts with four 5-ml. portions of 0.5 *N* hydrochloric acid. Discard the ether, and add the acid washes to the aqueous phase. Filter the aqueous phase through a pledget of cotton into a 50-ml. volumetric flask, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Haloperidol Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 245 mμ, with a suitable spectrophotometer, using 0.5 *N* hydrochloric acid in methanol (1 in 10) as the blank. Calculate the quantity, in mg., of $C_{21}H_{23}ClFNO_2$ in the portion of Solution taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and Storage—Preserve Haloperidol Solution in tight, light-resistant containers.

Solution available—Haloperidol Solution usually available contains the following amount of haloperidol: 2.0 mg. per ml.

CATEGORY and DOSE—See Haloperidol.

Haloperidol Tablets

Haloperidol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount $C_{21}H_{23}ClFNO_2$.

Identification—The solution prepared for measurement of absorbance in the *Assay* exhibits a maximum at 245 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Haloperidol Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Haloperidol Tablets meet the requirements of the content uniformity test for tablets using the following special procedure: Quantitatively transfer a finely powdered tablet to a suitable volumetric flask to provide a solution containing about 20 mcg. per ml. Add warm methanol and shake for 15 minutes. Dilute to volume with methanol, and filter, discarding the first 20 ml. of filtrate. Concomitantly determine the absorbance of the sample solution and of a solution of NF Haloperidol Reference Standard, in the same medium, at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 245 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{21}H_{23}ClFNO_2$ in the Tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of haloperidol in the tablet; D is the exact concentration, in mcg. per ml., of the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—(NOTE: Use sulfuric acid that has been saturated with chloroform.) Weigh and finely powder not less than 20 Haloperidol Tablets. Weigh accurately a portion of powder, equivalent to about 2.5 mg. of haloperidol, and transfer to a glass-stoppered flask. Add 25 ml. of 0.1 *N* sodium hydroxide and 50.0 ml. of chloroform, and shake for 30 minutes. Centrifuge the mixture, remove the aqueous layer, and transfer 25.0 ml. of the chloroform layer to a glass-stoppered flask. Add 50.0 ml. of 0.1 *N* sulfuric acid, shake for 15 minutes and centrifuge. Concomitantly determine the absorbance of the acid layer and of a solution of NF Haloperidol Reference Standard, in 0.1 *N* sulfuric acid at a concentration of about 25 mcg. per ml., in 1-cm. cells, at the maximum at about 245 mμ, with a suitable spectrophotometer, using 0.1 *N* sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{21}H_{23}ClFNO_2$ in the portion of the tablets taken by the formula $0.1\,C \times (A_U/A_S)$, in which C is the exact concentration in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Haloperidol Tablets in tight, light-resistant containers.

Tablets available—Haloperidol Tablets usually available contain the following amounts of haloperidol: 0.5, 1, 2, and 5 mg.

CATEGORY and DOSE—See Haloperidol.

Hexavitamin Capsules

Hexavitamin Capsules contain, in each capsule, not less than 1.5 mg. (5000 USP Units) of vitamin A in the form of retinol; not less than 10 mcg. (400 USP Units) of vitamin D from natural sources or as ergocalciferol or cholecalciferol or the products obtained by the activation of either ergosterol or 7-dehydrocholesterol; not less than 75 mg. of ascorbic acid ($C_6H_8O_6$); not less than 2 mg. of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS.HCl$) or an equivalent amount of thiamine mononitrate ($C_{12}H_{17}N_5O_4S$); not less than 3 mg. of riboflavin ($C_{17}H_{20}N_4O_6$); and not less than 20 mg. of niacinamide ($C_6H_6N_2O$).

Assay for vitamin A—Transfer to a saponification flask not less than 5 Hexavitamin Capsules, add 10 to 20 ml. of water, and heat for about 10 minutes. Crush any remaining solids with the blunt end of a glass rod and proceed as directed in the paragraph titled *Saponification* under *Vitamin A Assay,* page 891, beginning with "Boil under a reflux condenser . . . ."

Assay for vitamin D—Transfer to a saponification flask not less than 5 Hexavitamin Capsules, add 10 to 20 ml. of water, and heat for about 10 minutes. Crush any remaining solids with the blunt end of a glass rod and proceed as directed under *Vitamin D Assay, Chemical Method,* page 895.

The *Sample Preparation* used in the chromatographic procedure must contain not more than the equivalent of 7.5 mg. of vitamin A or less than 25 mcg. of vitamin D. If the ratio of vitamin A to vitamin D in the sample exceeds 300 to 1, proceed as directed under *Vitamin D Assay, Biological Method,* page 895.

Assay for ascorbic acid—Add not less than 10 Hexavitamin Capsules to 75 ml. of metaphosphoric-acetic acids T.S., and heat rapidly to not over 90°, with continuous swirling, until complete disintegration occurs. Transfer the suspension to a 500-ml. glass-stoppered volumetric flask containing 125 ml. of unheated metaphosphoric-acetic acids T.S., and immediately cool rapidly to room temperature. Transfer any remaining residue by rinsing with four or five successive, 10-ml. portions of the extracting solution, and add water to make 500.0 ml. Transfer, if necessary, any solid fatty material to the wall of the flask above the calibration line, using a dry glass rod so as not to affect the volume of the water solution. After thorough mixing, the fatty solids may be removed. Use an aliquot that will consume not less than 20 ml. of standard dichlorophenol-indophenol solution, and titrate with standard dichlorophenol-indophenol solution (see *Volumetric Solutions,* USP XVIII) until a pink color persists for at least 5 seconds. Correct for the volume of the dichlorophenol-indophenol solution consumed by a mixture of 5.5 ml. of the metaphosphoric-acetic acids T.S. and 15 ml. of water.

From the ascorbic acid equivalent of the standard dichlorophenol-indophenol solution, calculate the content of $C_6H_8O_6$ in each Capsule.

Assay for niacinamide—Proceed as directed under *Niacin or Niacinamide Assay, Chemical Method,* page 818, using *Standard Niacinamide Preparation* as the *Standard Preparation* in the *Assay Procedure,* and the following as the *Sample Preparation:* Transfer not less than 10 Hexavitamin Capsules to a 1000-ml. volumetric flask. Add about 200 ml. of water and place the flask on a steam bath for 1 hour. Cool to room temperature, add 10 ml. of a mixture of equal volumes of ether and solvent hexane, and shake well. Add sufficient water to make the aqueous phase 1000.0 ml., and shake well. Allow the solvent mixture to rise to the top and remove the solvent by suction. Transfer an aliquot containing about 1 mg. of niacinamide (V ml.) to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Calculate the quantity, in mg., of $C_6H_6N_2O$ in each capsule by the formula $(A_U/A_S) \times [1000/(V \times \text{No. of capsules taken})]$, in which V is the volume, in ml., of the aliquot of the sample used for final dilution to 100.0 ml.

Assay for thiamine hydrochloride (or mononitrate)—Using not less than 10 Hexavitamin Capsules, proceed as directed under *Thiamine Assay*, page 881.

Assay for riboflavin—Using not less than 10 Hexavitamin Capsules, proceed as directed under *Riboflavin Assay*, page 859.

Packaging and storage—Preserve Hexavitamin Capsules in tight, light-resistant containers.

Labeling—The labeling shall include no claim based upon any quantity of vitamin in excess of that specified in this monograph.

Category—Multivitamin supplement.

Usual dose—To be determined by the physician according to the needs of the patient.

Hexavitamin Tablets

Hexavitamin Tablets contain, in each tablet, not less than 1.5 mg. (5000 USP Units) of vitamin A in the form of retinol; not less than 10 mcg. (400 USP Units) of vitamin D from natural sources or as ergocalciferol or cholecalciferol or the products obtained by the activation of either ergosterol or 7-dehydrocholesterol; not less than 75 mg. of ascorbic acid ($C_6H_8O_6$); not less than 2 mg. of thiamine hydrochloride ($C_{12}H_{17}ClN_4OS.HCl$) or an equivalent amount of thiamine mononitrate ($C_{12}H_{17}N_5O_4S$); not less than 3 mg. of riboflavin ($C_{17}H_{20}N_4O_6$); and not less than 20 mg. of niacinamide ($C_6H_6N_2O$).

Disintegration, page 878—The disintegration time limit for Hexavitamin Tablets is 30 minutes.

Weight variation, page 901—Hexavitamin Tablets meet the requirements of the weight variation test for tablets.

Assay for vitamin A—Transfer to a saponification flask not less than 5 Hexavitamin Tablets, add 10 to 20 ml. of water, and heat for about 10 minutes. Crush any remaining solids with the blunt end of a glass rod and proceed as directed in the paragraph titled *Saponification* under *Vitamin A Assay*, page 891, beginning with "Boil under a reflux condenser . . . ."

Assay for vitamin D—Transfer to a saponification flask not less than 5 Hexavitamin Tablets, add 10 to 20 ml. of water, and heat for about 10 minutes. Crush any remaining solids with the blunt end of a glass rod and proceed as directed under *Vitamin D Assay, Chemical Method*, page 895.

The *Sample Preparation* used in the chromatographic procedure must contain not more than the equivalent of 7.5 mg. of vitamin A or less than 25 mcg. of vitamin D. If the ratio of vitamin A to vitamin D in the sample exceeds 300 to 1, proceed as directed under *Vitamin D Assay, Biological Method*, page 895.

Assay for ascorbic acid—Grind not less than 10 Hexavitamin Tablets in a mortar, in sufficient metaphosphoric-acetic acids T.S., to make a paste. Transfer the paste to a 500-ml. volumetric flask with the aid of 225 ml. of metaphosphoric-acetic acids T.S., add water to make 500.0 ml., and proceed as directed in the *Assay for ascorbic acid* under *Hexavitamin Capsules*, page 339, beginning with "Use an aliquot . . . ."

Assay for niacinamide—Proceed as directed under *Niacin or Niacinamide Assay, Chemical Method*, page 818, using *Standard Niacinamide Preparation* as the *Standard Preparation* in the *Assay Procedure*, and the following as the *Sample Preparation*: Crush and finely powder, without appreciable loss, not less than 10 Hexavitamin Tablets. Transfer with the aid of water to a 1000-ml. volumetric flask. Add about 200 ml. of water. Heat, if necessary, and mix until the powder has completely dissolved. Cool and dilute to 1000.0 ml. with water. Transfer an aliquot containing about 1 mg. of niacinamide (V ml.) to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Calculate the quantity, in mg., of $C_6H_6N_2O$ in each tablet by the formula $(A_U/A_S) \times [1000/(V \times \text{No. of tablets taken})]$, in which V is the volume, in ml., of the aliquot of the sample used for final dilution to 100.0 ml.

Assay for thiamine hydrochloride (or mononitrate)—Using not less than 10 Hexavitamin Tablets, proceed as directed under *Thiamine Assay*, page 881.

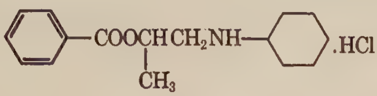
Assay for riboflavin—Using not less than 10 *Hexavitamin Tablets*, proceed as directed under *Riboflavin Assay*, page 859.

Packaging and storage—Preserve Hexavitamin Tablets in tight containers.

Labeling—The labeling shall include no claim based upon any quantity of vitamin in excess of that specified in this monograph.

Category and Dose—See Hexavitamin Capsules.

Hexylcaine Hydrochloride



1-(Cyclohexylamino)-2-propanol Benzoate (Ester) Hydrochloride

$C_{16}H_{23}NO_2 \cdot HCl$ Mol. wt. 297.83

Hexylcaine Hydrochloride, dried in vacuum over phosphorus pentoxide for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{16}H_{23}NO_2 \cdot HCl$.

Description—Hexylcaine Hydrochloride occurs as a white powder, having a bitter taste and not more than a slight aromatic odor.

Solubility—Hexylcaine Hydrochloride is soluble in water. It is freely soluble in alcohol and in chloroform, and practically insoluble in ether.

Identification—

A: To 5 ml. of a solution of Hexylcaine Hydrochloride (1 in 20) add 2 drops of diluted hydrochloric acid and 2 drops of a solution of sodium nitrite (1 in 10) and gradually mix with a solution of 200 mg. of betanaphthol in 10 ml. of a sodium hydroxide solution (1 in 10): a white precipitate forms which changes to a yellowish, oily mass (*distinction from the anesthetics responding to the diazo reaction*).

B: Dissolve about 100 mg. of Hexylcaine Hydrochloride in 10 ml. of water and divide the solution into two equal portions. To one portion add 2 ml. of ammonia T.S. and filter. Neutralize the clear filtrate with nitric acid and add 2 drops in excess: the solution responds to the tests for *Chloride*, page 808. To the second portion add 10 ml. of a saturated solution of picric acid and 2 drops of diluted sulfuric acid. Cool in a refrigerator for 30 minutes, filter, wash the precipitate with three 2-ml. portions of cold ether, and dry it at 105° for 15 minutes: the picrate so obtained melts between 129° and 133°, page 814. (*Caution: Picrates may be explosive.*)

Melting range, page 814—Hexylcaine Hydrochloride melts between 182° and 184°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Hexylcaine Hydrochloride, previously dried in vacuum over phosphorus pentoxide for 4 hours, exhibits maxima only at the same wavelengths as that of NF Hexylcaine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Hexylcaine Hydrochloride in 0.1 N hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Hexylcaine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the points of maximum absorbance occurring at about 232 mμ and 275 mμ do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Hexylcaine Hydrochloride (1 in 20) is between 4.0 and 6.0.

Acidity—Dissolve 1 g. of Hexylcaine Hydrochloride in 25 ml. of water, add methyl red T.S., and titrate with 0.02 N sodium hydroxide: not more than 0.5 ml. is required for neutralization.

Loss on drying, page 814—Dry Hexylcaine Hydrochloride in vacuum over phosphorus pentoxide for 4 hours: it loses not more than 0.2 percent of its weight.

Residue on ignition, page 858—Hexylcaine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Hexylcaine Hydrochloride in 15 ml. of water, add 1 ml. of 1 N hydrochloric acid, and dilute with water to 25 ml.: the heavy metals limit for Hexylcaine Hydrochloride is 30 parts per million.

Assay—Transfer about 100 mg. of Hexylcaine Hydrochloride, previously dried in vacuum over phosphorus pentoxide for 4 hours and accurately weighed, to a 100-ml. volumetric flask, dissolve in 0.1 N hydrochloric acid, dilute to volume with 0.1 N hydrochloric acid, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with 0.1 N hydrochloric acid, and mix. Transfer 10.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with 0.1 N hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Hexylcaine Hydrochloride Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml. in 1-cm. cells, at the maximum at about 232 mμ, with a suitable spectrophotometer, using 0.1 N hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{23}NO_2 \cdot HCl$ in the Hexylcaine Hydrochloride taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Hexylcaine Hydrochloride in tight containers.

Category—Local anesthetic.

Usual dose—Topically or by injection according to site and condition.

Hexylcaine Hydrochloride Injection

Hexylcaine Hydrochloride Injection is a sterile solution of hexylcaine hydrochloride in water for injection, with or without the addition of dextrose ($C_6H_{12}O_6 . H_2O$). It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{16}H_{23}NO_2 . HCl$(hexylcaine hydrochloride).

Identification—Hexylcaine Hydrochloride Injection responds to *Identification test B* under *Hexylcaine Hydrochloride*, page 341.

Ultraviolet absorption, page 866—Hexylcaine Hydrochloride Injection diluted with 0.1 *N* hydrochloric acid exhibits absorbance maxima at about 232 mμ and 275 mμ.

pH, page 824—The pH of Hexylcaine Hydrochloride Injection is between 3.0 and 5.0.

Other requirements—Hexylcaine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Dextrose—If dextrose is present, transfer an accurately measured volume of Hexylcaine Hydrochloride Injection, containing about 1 g. of dextrose, to a 50-ml. volumetric flask, add 0.2 ml. of ammonia T.S., dilute to volume with water, mix, and filter. Then after 30 minutes, determine the angular rotation of the filtrate in a 200-mm. tube at 25° (see page 822). The observed rotation, in degrees, multiplied by 0.5213, represents the weight, in g., of $C_6H_{12}O_6 . H_2O$ in the volume of the Injection taken. Hexylcaine Hydrochloride Injection contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_6H_{12}O_6 . H_2O$.

Assay—

Mixed solvent—Prepare a solution by mixing 8 ml. of methanol, 1 ml. of glacial acetic acid, 0.2 ml. of hydrochloric acid, and sufficient water-saturated chloroform to make 100 ml.

Standard preparation—Dissolve a suitable quantity of NF Hexylcaine Hydrochloride Reference Standard, accurately weighed, in the *Mixed solvent*, and prepare, by stepwise dilution, a solution containing about 200 mcg. in each ml., calculated on the dried basis.

Assay preparation—Transfer an accurately measured volume of Hexylcaine Hydrochloride Injection, equivalent to about 100 mg. of hexylcaine hydrochloride, to a 10-ml. volumetric flask, dilute to volume with water, and mix.

Preparation of the chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 250-mm. test tube to which is fused a 5-cm. length of 7-mm. tubing) with the aid of a tamping rod of stainless steel, aluminum, or glass, about 45 cm. long and having a disk with a diameter about 1 mm. less than that of the tube. To 2 g. of purified siliceous earth in a 100-ml. beaker, add 1 ml. of sulfamic acid solution (1 in 20), and mix until a fluffy mixture is obtained. Transfer the mixture to the chromatographic tube and tamp gently to compress the material to a uniform mass. Similarly, mix 4 g. of purified siliceous earth with a mixture of 2.0 ml. of the *Assay preparation* and 1 ml. of sulfamic acid solution (15 in 100), and transfer to the column. Dry-rinse the beaker with 1 g. of purified siliceous earth, transfer it to the column, and tamp. (The ether wash, in the *Procedure*, will pass through a properly prepared column in 5 to 10 minutes.)

Procedure—Wash the column with 100 ml. of water-saturated ether, and discard the washings. Place under the column, as a receiver, a 100-ml. volumetric flask containing 8 ml. of methanol and 0.2 ml. of hydrochloric acid. Pass through the column a mixture of 1 ml. of glacial acetic acid and 90 ml. of water-saturated chloroform. Mix the eluate, allow it to come to room temperature, dilute to volume with water-saturated chloroform, and mix. Concomitantly determine the absorbance of this solution (A_U) and of the *Standard preparation* (A_S) at the maximum absorbance at about 275 mμ, in 1-cm. cells with a suitable spectrophotometer, using the *Mixed solvent* as the blank.

Calculate the quantity, in mg., of $C_{16}H_{23}NO_2 . HCl$ in each ml. of the Injection taken by the formula $0.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Hexylcaine Hydrochloride Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Hexylcaine Hydrochloride Injection usually available contains the following amounts of hexylcaine hydrochloride: 1 percent in 30, 50, and 100 ml., 2 percent in 20 ml., 2.5 precent with 10 percent dextrose in 2 ml.

CATEGORY and DOSE—See Hexylcaine Hydrochloride.

Hexylcaine Hydrochloride Solution

Hexylcaine Hydrochloride Solution contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{16}H_{23}NO_2 . HCl$.

Description—Hexylcaine Hydrochloride Solution is a clear, colorless solution of hexylcaine hydrochloride in water.

Identification—Hexylcaine Hydrochloride Solution responds to *Identification test B* under *Hexylcaine Hydrochloride*, page 341.

pH, page 824—The pH of Hexylcaine Hydrochloride Solution is between 3.0 and 5.0.

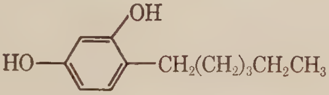
Assay—Proceed as directed in the *Assay* under *Hexylcaine Hydrochloride Injection*, page 342, using as the *Assay preparation* a solution prepared by diluting a volume of Hexylcaine Hydrochloride Solution, equivalent to about 500 mg. of hexylcaine hydrochloride, with sufficient water to make 50.0 ml. Calculate the quantity, in mg., of $C_{16}H_{23}NO_2 . HCl$ in each ml. of the Solution taken by the formula $2.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Solution taken.

Packaging and storage—Preserve Hexylcaine Hydrochloride Solution in tight containers.

Solution available—Hexylcaine Hydrochloride Solution usually available contains the following amount of hexylcaine hydrochloride: 5 percent.

CATEGORY and DOSE—See Hexylcaine Hydrochloride.

Hexylresorcinol



4-Hexylresorcinol

$C_{12}H_{18}O_2$ Mol. wt. 194.28

Hexylresorcinol, dried over silica gel for 4 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{12}H_{18}O_2$.

Caution: Hexylresorcinol is irritating to the oral mucosa and respiratory tract and to the skin, and its solution in alcohol has vesicant properties.

Description—Hexylresorcinol occurs as white, or yellowish white, needle-shaped crystals. It has a faint odor and a sharp, astringent taste, and produces a sensation of numbness when placed on the tongue. It acquires a brownish pink tint on exposure to light and air.

Solubility—Hexylresorcinol is very slightly soluble in water. It is freely soluble in alcohol, in methanol, in glycerin, in ether, in chloroform, in benzene, and in vegetable oils.

Identification—

A: To 1 ml. of a saturated solution of Hexylresorcinol add 1 ml. of nitric acid: a light red color appears.

B: To 1 ml. of a saturated solution of Hexylresorcinol add 1 ml. of bromine T.S.: a yellow, flocculent precipitate forms. Add 2 ml. of ammonia T.S.: the precipitate dissolves, producing a solution with a yellow color.

Melting range, page 814—Hexylresorcinol melts between 62° and 67°.

Acidity—Dissolve 250 mg. of Hexylresorcinol in 500 ml. of water, add methyl red T.S., and titrate with 0.02 *N* sodium hydroxide: not more than 1 ml. is required for neutralization.

Residue on ignition, page 858—Hexylresorcinol yields not more than 0.1 percent of residue on ignition.

Resorcinol and other phenols—Shake about 1 g. of Hexylresorcinol with 50 ml. of water for a few minutes, filter, and to the filtrate add 3 drops of ferric chloride T.S.: no red or blue color is produced.

Assay—Dissolve 70 to 100 mg. of Hexylresorcinol, previously dried over silica gel for 4 hours and accurately weighed, in 10 ml. of methanol in a 250-ml. iodine flask. Add 30.0 ml. of 0.1 *N* bromine, then add quickly 5 ml. of hydrochloric acid, and stopper the flask immediately. Cool the flask under running water to room temperature, shake it vigorously for 5 minutes, then set it aside for 5 minutes. Cautiously loosen the stopper, add 6 ml. of potassium iodide T.S. around the stopper, again stopper tightly, and swirl gently. Add 1 ml. of chloroform, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, adding 3 drops of starch T.S. as the end-point is neared. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 0.1 *N* bromine is equivalent to 4.857 mg. of $C_{12}H_{18}O_2$.

Packaging and storage—Preserve Hexylresorcinol in tight, light-resistant containers.

CATEGORY—Anthelmintic (intestinal roundworms and trematodes).

USUAL DOSE—**1 g.** May repeat at weekly intervals if necessary.

Hexylresorcinol Pills

Hexylresorcinol Pills consist of hexylresorcinol covered with a rupture-resistant coating that is dispersible in the digestive tract. Hexylresorcinol Pills contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{12}H_{18}O_2$.

Identification—Carefully remove the coating from a sufficient number of Hexylresorcinol Pills, and triturate a quantity of the contents, equivalent to about 100 mg. of hexylresorcinol, with about 10 ml. of solvent hexane. Transfer the mixture, with the aid of 15 ml. of solvent hexane, to a small flask, attach a reflux condenser, and reflux for 15 minutes. Filter the liquid while hot, and place it in a refrigerator for 2 hours. Collect the precipitate of hexylresorcinol on a filter, drain thoroughly with the aid of suction, wash with several successive 1-ml. portions of solvent hexane, and dry with a current of air: the hexylresorcinol so obtained melts between 62° and 67°, page 814, and responds to the *Identification tests* under *Hexylresorcinol,* page 343.

Rupture resistance—Place 50 Hexylresorcinol Pills each in turn upon a hard surface, and apply pressure gradually up to a total of 10 kg. by means of a suitable press. After releasing the pressure place each pill in a small test tube, cover with 5 ml. of alcohol, and allow to stand for 5 minutes. Remove the pill, evaporate the alcohol nearly to dryness, and take up the residue with 10 ml. of water. Add 3 drops of bromine T.S., shake vigorously, and add ammonia T.S. dropwise: the yellow color is discharged. If more than 2 Pills fail the test, repeat the test upon 50 additional Pills: the total number of failures in the 100 Pills taken for the test does not exceed 6.

Disintegration, page 878—The disintegration time limit for Hexylresorcinol Pills is 4 hours, simulated gastric fluid T.S. being substituted for water in the test.

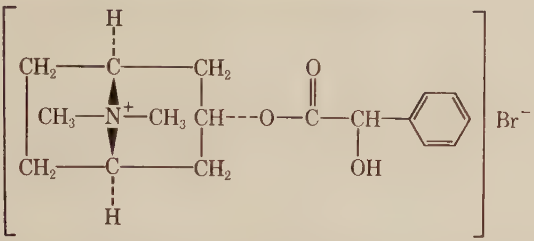
Assay—Weigh and finely powder not less than 20 Hexylresorcinol Pills. Weigh accurately a portion of the powder, equivalent to about 800 mg. of hexylresorcinol, triturate well with 25 ml. of methanol, and decant through a filter into a 100-ml. volumetric flask. Triturate the residue in the mortar with 15 ml. of methanol, decant through the same filter, and completely transfer the residue to the filter. Wash the mortar and the filter with successive portions of methanol until the total filtrate measures about 95 ml., then add methanol to volume, and mix. Pipet 10.0 ml. of the methanol solution to a 250-ml. iodine flask, and proceed as directed in the *Assay* under *Hexylresorcinol,* page 343, beginning with "Add 30.0 ml. of 0.1 *N* bromine . . . ."

Packaging and storage—Preserve Hexylresorcinol Pills in well-closed containers.

Pills available—Hexylresorcinol Pills usually available contain the following amounts of hexylresorcinol: 100 and 200 mg.

CATEGORY and DOSE—See Hexylresorcinol.

Homatropine Methylbromide



3α-Hydroxy-8-methyl-1αH,5αH-tropanium Bromide Mandelate

$C_{17}H_{24}BrNO_3$ Mol. wt. 370.29

Homatropine Methylbromide contains not less than 98.5 percent and not more than 100.5 percent of $C_{17}H_{24}BrNO_3$, calculated on the dried basis.

Description—Homatropine Methylbromide occurs as a white, odorless powder. It slowly darkens on exposure to light.

Solubility—Homatropine Methylbromide is very soluble in water. It is freely soluble in alcohol. It is practically insoluble in ether and in acetone, but is freely soluble in acetone containing about 20 percent of water.

Identification—

A: Mercuric-potassium iodide T.S. produces in a solution of Homatropine Methylbromide (1 in 50) a white or slightly yellowish precipitate, but no precipitation is caused by solutions of alkali hydroxides or carbonates, even in concentrated solutions of the substance (distinction from most alkaloids).

B: To a solution of Homatropine Methylbromide (1 in 50) add ammonium reineckate T.S.: a red precipitate is formed.

C: A solution of Homatropine Methylbromide (1 in 20) responds to the tests for *Bromide,* page 808.

Melting range, *Class Ia,* page 815—Homatropine Methylbromide melts between 190° and 198°, the temperature at which distinct liquefaction of the sample is first observed being taken as the beginning of melting.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Homatropine Methylbromide, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Homatropine Methylbromide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 1000 solution of Homatropine Methylbromide in alcohol exhibits maxima and minima at the same wavelengths as that of NF Homatropine Methylbromide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance occurring at about 258 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Homatropine Methylbromide (1 in 100) is between 4.5 and 6.5.

Loss on drying, page 814—Dry Homatropine Methylbromide at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 250 mg. of Homatropine Methylbromide is negligible.

Homatropine, atropine, and other solanaceous alkaloids—To 1 ml. of a solution of Homatropine Methylbromide (1 in 50) add a few drops of ammonia T.S., shake the solution with 5 ml. of chloroform, and evaporate the separated chloroform layer on a steam bath to dryness. Warm the residue with 1.5 ml. of a solution made by dissolving 500 mg. of mercuric chloride in 25 ml. of a mixture of 5 volumes of alcohol and 3 volumes of water: no yellow or red color develops.

Assay—Dissolve about 700 mg. of Homatropine Methylbromide, accurately weighed, in a mixture of 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 37.03 mg. of $C_{17}H_{24}BrNO_3$.

Packaging and storage—Preserve Homatropine Methylbromide in tight, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**2.5** to **5 mg.** four times a day.

Homatropine Methylbromide Tablets

Homatropine Methylbromide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{24}BrNO_3$.

Identification—Shake a quantity of finely powdered Homatropine Methylbromide Tablets, representing about 10 mg. of homatropine methylbromide, with 15 ml. of a mixture of equal volumes of methanol and water for 10 minutes, and filter. Evaporate the filtrate on a steam bath to dryness, and dry at 105° for 1 hour. The residue of homatropine methylbromide so obtained melts between 190° and 198°, page 814, the temperature at which distinct liquefaction of the sample is first observed being taken as the beginning of melting.

Disintegration, page 878—The disintegration time limit for Homatropine Methylbromide Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Homatropine Methylbromide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure:

Standard preparation—Transfer about 25 mg. of NF Homatropine Methylbromide Reference Standard, accurately weighed, to a 50-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a second 50-ml. volumetric flask, dilute to volume with water, and mix.

Test preparation—Transfer a finely powdered tablet to a volumetric flask, suitably sized such that the concentration, when diluted to volume, is equivalent to about 100 mcg. of homatropine methylbromide per ml. Add water to about one-half of the volume of the flask, shake for 10 minutes, dilute to volume with water, mix, and filter, discarding the first 10 ml. of filtrate. Use the subsequent filtrate as directed in the *Procedure*.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 50-ml. volumetric flasks. To each flask add 0.1 ml. of 2.5 *N* sodium hydroxide, and heat in a water bath at 80° for 15 minutes. Cool to room temperature, add 2.0 ml. of 0.2 *M* ceric ammonium sulfate in 1 *N* sulfuric acid, and mix. To each flask add 20.0 ml. of *n*-hexane, and shake for 15 minutes. Decant the hexane layers into separate 1-cm. cells, and concomitantly determine the absorbances of the solutions at the maximum at about 242 mμ, with a suitable spectrophotometer, using *n*-hexane as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Test preparation* as A_U. Calculate the quantity, in mg., of $C_{17}H_{24}BrNO_3$ in the tablet by the formula $(T/D) \times C\,(A_U/A_S)$, in which T is the labeled quantity of homatropine methylbromide, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of the *Test preparation* based upon the labeled quantity per tablet and the extent of dilution; and C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Assay—

Standard preparation—Weigh accurately about 25 mg. of NF Homatropine Methylbromide Reference Standard, previously dried at 105° for 3 hours, and dissolve it in water to make 50.0 ml.

Assay preparation—Weigh and finely powder not less than 20 Homatropine Methylbromide Tablets. Weigh accurately a portion of the powder, equivalent to about 12.5 mg. of homatropine methylbromide, and shake it with 10 ml. of water at frequent intervals during 30 minutes. Filter under reduced pressure through a sintered-glass crucible into a test tube placed in the suction flask under the filtering funnel, and wash under suction with several small portions of water. Transfer the contents of the test tube to a 25-ml. volumetric flask, add water to volume, and mix.

Procedure—Pipet 10.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate test tubes, to each add 1 ml. of dilute sulfuric acid (1 in 7) and 2 ml. of ammonium reineckate T.S., shake gently but well, and allow to stand for 1 hour. Filter through a sintered-glass crucible with suction, using portions of the filtrate to transfer the precipitate completely to the filter, and wash it with three 2-ml. portions of ice-cold water. Completely dissolve the precipitate by pouring over it 1-ml. portions of acetone with the application of suction, receiving the solution in a 10-ml. volumetric flask, add acetone to volume, and mix. Concomitantly determine the absorbance of each solution with a suitable spectrophotometer at the maximum at about 525 mμ, using acetone as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S, and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{17}H_{24}BrNO_3$ in the portion of the Tablets taken by the formula $0.025C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Homatropine Methylbromide Tablets in tight, light-resistant containers.

Tablets available—Homatropine Methylbromide Tablets usually available contain the following amounts of Homatropine Methylbromide: 2.5 and 5 mg.

CATEGORY and DOSE—See Homatropine Methylbromide.

Hyaluronidase for Injection

Hyaluronidase for Injection is a sterile, dry, soluble, enzyme product prepared from mammalian testes and capable of hydrolyzing mucopolysaccharides of the type of hyaluronic acid. Its potency, in NF Hyaluronidase Units, is not less than the labeled potency. Hyaluronidase for Injection contains not more than 0.25 mcg. of tyrosine for each NF Hyaluronidase Unit. It may contain a suitable stabilizer.

Description—Hyaluronidase for Injection is a white, amorphous solid. It is destroyed by heat. Its solutions are colorless and odorless.

Tyrosine—Dissolve the entire contents of 1 or more containers of Hyaluronidase for Injection in sufficient water, accurately measured, to give a concentration of about 60 NF Hyaluronidase Units per ml. Pipet 2.0 ml. of the solution into a 15-ml. centrifuge tube calibrated at 6 ml., and evaporate at 105° to dryness. Add 0.2 ml. of 6 N sodium hydroxide, and heat with steam under pressure at 121° for 3 hours. Add 0.3 ml. of 7 N sulfuric acid, then add 1.5 ml. of water and 1.5 ml. of a 15 in 100 solution of mercuric sulfate in 5 N sulfuric acid. Heat in a steam bath for 10 minutes, and cool to room temperature. Add 1 ml. of 7 N sulfuric acid and 1 ml. of sodium nitrite solution (1 in 500), with shaking. Add water to make 6 ml., mix, centrifuge, and decant the supernatant liquid. Twenty minutes after diluting to 6-ml. volume, determine the absorbance of the supernatant liquid at 540 mμ, with a suitable spectrophotometer.

Repeat the preceding test, using the same quantities of the same reagents and in the same manner but omitting the Hyaluronidase for Injection and replacing the 1.5 ml. of water with 1.5 ml. of a solution of NF Tyrosine Reference Standard in 0.4 N sulfuric acid containing 30 mcg. in each ml.

Calculate the quantity, in mcg., of tyrosine in the 2-ml. aliquot of the solution of Hyaluronidase for Injection by the formula $45 \times (A_U/A_S)$, in which A_U is the absorbance of the solution prepared from the Hyaluronidase for Injection and A_S is that of the solution of NF Tyrosine Reference Standard: not more than 0.25 mcg. of tyrosine is found for each Unit of hyaluronidase.

Pyrogen—Hyaluronidase for Injection meets the requirements of the *Pyrogen Test*, page 851, the test dose being 1.0 ml. per kg., of a solution containing 75 NF Hyaluronidase Units in each ml.

Sterility—Hyaluronidase for Injection meets the requirements under *Sterility Tests*, page 874.

Assay—

Acetate buffer solution—Dissolve 14 g. of potassium acetate and 20.5 ml. of glacial acetic acid in sufficient water to make 1000 ml.

Phosphate buffer solution—Dissolve 2.5 g. of sodium biphosphate, 1.0 g. of anhydrous sodium phosphate, and 8.2 g. of sodium chloride in sufficient water to make 1000 ml.

Hydrolyzed gelatin—Dissolve 50 g. of bacteriological gelatin in 1000 ml. of water, heat in an autoclave at 121° for 90 minutes, and freeze-dry the solution.

Diluent for hyaluronidase solutions—Mix 250 ml. of *Phosphate buffer solution* with 250 ml. of water and, within 2 hours before use, dissolve 330 mg. of *Hydrolyzed gelatin* in the mixture.

Serum stock solution—Reconstitute dried horse serum with water to its original volume, and dilute it with 9 volumes of *Acetate buffer solution*. Adjust the pH to 3.1 with 4 N hydrochloric acid, and allow the solution to stand at room temperature for 18 to 24 hours. Store the solution at 0° to 4°, and use within 30 days.

Serum solution—On the day of the assay, dilute 1 volume of *Serum stock solution* with 3 volumes of *Acetate buffer solution*, and adjust to room temperature.

Potassium hyaluronate stock solution—Prepare a stock solution to contain, in each ml., 500 mcg. of potassium hyaluronate, previously dried in vacuum over phosphorus pentoxide for 48 hours. The use of a weighing bottle is desirable. Store the solution at a temperature not above 5°, and use within 30 days. Do not keep the hyaluronate over phosphorus pentoxide indefinitely.

Hyaluronate solution—On the day of the assay, dilute 1 volume of *Potassium hyaluronate stock solution* with 1 volume of *Phosphate buffer solution*.

Standard solution—Dissolve a suitable quantity of NF Hyaluronidase Reference Standard, accurately weighed, in sufficient cold *Diluent for hyaluronidase solutions* to provide a solution of known concentration containing about 1.5 NF Hyaluronidase Units in each ml. Prepare this solution immediately before use in the assay.

Assay solution—Dissolve the contents of the container of Hyaluronidase for Injection by adding cold *Diluent for hyaluronidase solutions* directly to the container. On the basis of trial or experience dilute the solution so prepared with cold *Diluent for hyaluronidase solutions* so that the observed absorbances with the three dilutions of Hyaluronidase for Injection will fall on the upper, linear part of the standard curve prepared as directed below.

Procedure—Prepare a standard concentration-response curve by adding to each of twelve 16 × 100-mm. test tubes 0.50 ml. of *Hyaluronate solution*. To each of two of the tubes add, respectively, 0.50 ml., 0.40 ml., 0.30 ml., 0.20 ml., 0.10 ml., and none, of *Diluent for hyaluronidase solutions*. If quantities of *Standard solution* other than those indicated below are used, change the above-specified quantities of *Diluent for hyaluronidase solutions* so that the final volume of solution in each tube, after the addition of the *Standard solution*, will be 1.00 ml.

On a rigid time schedule, add to each of two tubes, at half-minute intervals, none, 0.10 ml., 0.20 ml., 0.30 ml., 0.40 ml., and 0.50 ml., respectively, of *Standard solution*. Mix the contents by gentle shaking, and place each tube in a water bath maintained at 37 ± 0.2°. After 30 ± 0.25 minutes, remove each tube, in order, from the water bath at half-minute intervals, and immediately add 4.0 ml. of *Serum solution*. Shake the tube, and allow it to stand at room temperature for 30 ± 2 minutes. Then shake the tube, and determine the absorbance at 640 mμ, with a suitable spectrophotometer. Perform a blank determination but omit the hyaluronate, and make any necessary correction. Plot the average absorbance value for each level against the hyaluronidase activity expressed in Units, and draw the smooth curve which best fits the plotted points.

Concurrently, to six test tubes add 0.50 ml. of *Hyaluronate solution* and sufficient *Diluent for hyaluronidase solutions* so that the final volume, after the addition of the *Assay solution*, is 1.00 ml. Add, at half-minute intervals, sufficient *Assay solution* so that duplicate tubes contain about 0.30, 0.50, and 0.70 Units, respectively. Shake each tube gently, and treat as directed in the preceding paragraph for the Standard, beginning with "place each tube in a water bath." Measure the absorbance in the spectrophotometer, and make any necessary correction for the blank. The potency of Hyaluronidase for Injection is given by the average of the six activity values read from the standard curve.

Packaging and storage—Preserve Hyaluronidase for Injection in *Containers for Sterile Solids* as described under *Injections*, page 810, preferably of Type I or Type III glass, in a cool, dry place.

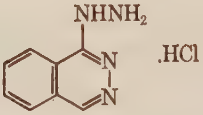
Labeling—Hyaluronidase for Injection complies with the requirements for *Labeling* under *Injections*, page 810.

Sizes available—Hyaluronidase for Injection is usually available in the following amounts: 150 and 1500 NF Hyaluronidase Units.

CATEGORY—Spreading agent.

USUAL DOSE—Hypodermoclysis, **150 NF Units.**

Hydralazine Hydrochloride



1-Hydrazinophthalazine Monohydrochloride

$C_8H_8N_4 . HCl$ Mol. wt. 196.64

Hydralazine Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_8H_8N_4 . HCl$, calculated on the dried basis.

Description—Hydralazine Hydrochloride occurs as a white, odorless, crystalline powder.

Solubility—Hydralazine Hydrochloride is soluble in water and is slightly soluble in alcohol. It is very slightly soluble in ether.

Identification—

A: A solution of Hydralazine Hydrochloride (1 in 4000) responds to the tests for *Chloride*, page 808.

B: To 5 ml. of a solution of Hydralazine Hydrochloride (1 in 100) add 5 ml. of a solution of *o*-nitrobenzaldehyde in alcohol (1 in 50): an orange precipitate is formed.

Melting range, *Class Ia*, page 815—Hydralazine Hydrochloride melts between 270° and 280° with decomposition.

Loss on drying, page 814—Dry Hydralazine Hydrochloride in vacuum over phosphorus pentoxide for 8 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 878—Hydralazine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Water-insoluble substances—Transfer 2 g. of Hydralazine Hydrochloride to a

250-ml. conical flask, add 100 ml. of water, and shake mechanically for about 30 minutes. Filter the solution through a tared sintered-glass crucible and wash into the crucible any undissolved residue remaining in the flask. Wash the residue with three 10-ml. portions of water, dry at 105° for about 3 hours, cool, and weigh: the weight of the residue does not exceed 10 mg. (0.5 percent).

Assay—Transfer to a 250-ml. iodine flask about 150 mg. of Hydralazine Hydrochloride, accurately weighed, and dissolve it in 25 ml. of water. Add 25 ml. of hydrochloric acid, cool to room temperature, add 5 ml. of chloroform, and titrate with 0.02 *M* potassium iodate until the purple color of iodine disappears from the chloroform. The last portion of the iodate solution must be added dropwise, the mixture being agitated vigorously and continuously. Each ml. of 0.02 *M* potassium iodate is equivalent to 3.933 mg. of $C_8H_8N_4.HCl$.

Packaging and storage—Preserve Hydralazine Hydrochloride in tight containers.

CATEGORY—Antihypertensive.

USUAL DOSE RANGE—Oral, Initial, **10 mg.** four times a day. Maintenance, up to **100 mg.** four times a day. Intramuscular or intravenous, **20** to **40 mg.** repeated as necessary.

Hydralazine Hydrochloride Injection

Hydralazine Hydrochloride Injection is a sterile solution of hydralazine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_8N_4.HCl$.

Identification—Hydralazine Hydrochloride Injection responds to *Identification test B* under *Hydralazine Hydrochloride*, page 348.

Other requirements—Hydralazine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—Transfer to a 250-ml. iodine flask an accurately measured amount of Hydralazine Hydrochloride Injection, equivalent to about 100 mg. of hydralazine hydrochloride, add 20 ml. of hydrochloric acid, and proceed as directed in the *Assay* under *Hydralazine Hydrochloride*, page 348, beginning with "... cool to room temperature ...."

Packaging and storage—Preserve Hydralazine Hydrochloride Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injection available—Hydralazine Hydrochloride Injection usually available contains the following amount of hydralazine hydrochloride: 20 mg. in 1 ml.

CATEGORY and DOSE—See Hydralazine Hydrochloride.

Hydralazine Hydrochloride Tablets

Hydralazine Hydrochloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_8N_4.HCl$.

Identification—Extract a quantity of finely powdered Hydralazine Hydrochloride Tablets, equivalent to about 100 mg. of hydralazine hydrochloride, with two 25-ml. portions of methanol. Filter the combined methanol extracts, and evaporate to dryness on a steam bath: the residue of hydralazine hydrochloride so obtained responds to *Identification test B* under *Hydralazine Hydrochloride*, page 348.

Disintegration, page 878—The disintegration time limit for Hydralazine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Hydralazine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 50-ml. volumetric flask with the aid of 25 ml. of dilute methanol (1 in 2). Shake mechanically for 10 minutes, dilute to volume with dilute methanol (1 in 2), and mix. Filter, and discard the first 5 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with water to provide a solution containing approximately 10 mcg. of hydralazine hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Hydralazine Hydrochloride Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 260 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_8H_8N_4.HCl$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of hydralazine hydrochloride, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of hydralazine hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 25 Hydralazine Hydrochloride Tablets. Transfer to a 500-ml. iodine flask an accurately weighed amount of the powder, equivalent to about 150 mg. of hydralazine hydrochloride, add 100 ml. of water, and shake mechanically for 15 minutes. Add 40 ml. of hydrochloric acid, and proceed as directed in the *Assay* under *Hydralazine Hydrochloride,* page 348, beginning with "... cool to room temperature. ..."

Packaging and storage—Preserve Hydralazine Hydrochloride Tablets in tight containers.

Tablets available—Hydralazine Hydrochloride Tablets usually available contain the following amounts of hydralazine hydrochloride: 10, 25, 50, and 100 mg.

CATEGORY and DOSE—See Hydralazine Hydrochloride.

Diluted Hydrochloric Acid

Diluted Hydrochloric Acid contains, in each 100 ml., not less than 9.5 g. and not more than 10.5 g. of HCl. Diluted Hydrochloric Acid may be prepared as follows:

Hydrochloric Acid	**234 ml.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Mix the ingredients.

Description—Diluted Hydrochloric Acid is a colorless, odorless liquid. Its specific gravity is about 1.05.

Identification—Diluted Hydrochloric Acid responds to the tests for *Chloride,* page 808.

Residue on ignition, page 858—To 20 ml. of Diluted Hydrochloric Acid add 2 drops of sulfuric acid, evaporate to dryness, and ignite: not more than 2 mg. of residue remains.

Free bromine or chlorine—Add 1 ml. of potassium iodide T.S. and 1 ml. of chloroform to 10 ml. of Diluted Hydrochloric Acid, and agitate the mixture: the chloroform remains free from any violet coloration for at least 1 minute.

Sulfate—To a mixture of 3 ml. of Diluted Hydrochloric Acid and 5 ml. of water add 5 drops of barium chloride T.S.: neither turbidity nor precipitate appears within 1 hour.

Sulfite—On the completion of the test for *Sulfate,* the further addition to the liquid of 2 drops of 0.1 N iodine produces neither turbidity nor decolorization of the iodine.

Arsenic—A 16.7-ml. portion of Diluted Hydrochloric Acid meets the requirements of the *Arsenic Test,* page 777 (0.6 part per million As).

Heavy metals, page 806—To 9.5 ml. (10 g.) of Diluted Hydrochloric Acid add 5 ml. of water and 1 drop of phenolphthalein T.S. Add ammonia T.S. until the solution assumes a faint pink color. Add 2 ml. of diluted acetic acid, and water to make 25 ml.: the heavy metals limit for Diluted Hydrochloric Acid is 5 parts per million.

Assay—Transfer 10.0 ml. of Diluted Hydrochloric Acid to a conical flask, and add about 20 ml. of water. Add 3 drops of methyl red T.S., and titrate the solution with 1 N sodium hydroxide. Each ml. of 1 N sodium hydroxide is equivalent to 36.46 mg. of HCl.

Packaging and storage—Preserve Diluted Hydrochloric Acid in tight containers.

CATEGORY—Acidifier (gastric).

USUAL DOSE—**5 ml.,** well diluted in water.

Hydrocortisone Lotion

Hydrocortisone Lotion is hydrocortisone in a suitable aqueous vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{30}O_5$.

Identification—Transfer a quantity of Hydrocortisone Lotion, equivalent to about 5 mg. of hydrocortisone, to a separator containing 10 ml. of methylene chloride, shake for 1 minute, and allow the layers to separate. Filter the methylene chloride extract onto a suitable chromatographic column that has been packed with 2 g. of a suitable activated magnesium silicate. Wash the column with 25 ml. of methylene chloride, with the aid of slight air pressure, discarding the washings, and elute the hydrocortisone with 10 ml. of methanol. Spot a 10-μl. portion of the eluate and 10 μl. of a solution in methanol containing 500 mcg. per ml. of USP Hydrocortisone Reference Standard on a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of 180 parts of chloroform, 15 parts of methanol, and 1 part of water until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under shortwave ultraviolet light: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Assay—

Standard preparation—Prepare as directed for *Standard preparation* under *Steroid Assay*, page 876, using USP Hydrocortisone Reference Standard.

Assay preparation—Transfer to a separator an accurately weighed quantity of Hydrocortisone Lotion, equivalent to about 20 mg. of hydrocortisone, and add 15 ml. of water. Extract with four 25-ml. portions of chloroform, filtering each portion through chloroform-washed cotton into a 200-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 20.0 ml. of this solution into a 100-ml. volumetric flask, add chloroform to volume, and mix. Pipet 10.0 ml. of the resulting solution into a glass-stoppered, 50-ml. conical flask, evaporate on a steam bath just to dryness, cool, and dissolve the residue in 20.0 ml. of alcohol.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{21}H_{30}O_5$ in the portion of the Lotion taken by the formula $2C \times (A_U/A_S)$.

Packaging and storage—Preserve Hydrocortisone Lotion in tight containers.

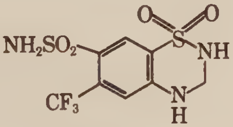
Lotions available—Hydrocortisone Lotion usually available contains hydrocortisone in the following concentrations: 0.125, 0.25, 0.5, and 1 percent.

CATEGORY—Glucocorticoid.

APPLICATION—Topically, to the affected area as a 0.125, 0.25, 0.5, or 1 percent lotion three or four times a day.

Hydrocortisone and Iodochlorhydroxyquin Cream, page 371
Hydrocortisone and Iodochlorhydroxyquin Lotion, page 372
Hydrocortisone and Iodochlorhydroxyquin Ointment, page 373
Hydrocortisone Acetate and Neomycin Sulfate Lotion, page 474

Hydroflumethiazide*



3,4-Dihydro-6-(trifluoromethyl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide

$C_8H_8F_3N_3O_4S_2$ Mol. wt. 331.29

Hydroflumethiazide contains not less than 98.0 percent and not more than 102.0 percent of $C_8H_8F_3N_3O_4S_2$, calculated on the anhydrous basis.

Description—Hydroflumethiazide occurs as a white to cream colored, finely divided, crystalline powder. It is odorless.

Solubility—Hydroflumethiazide is very slightly soluble in water. It is soluble in alcohol, and is freely soluble in acetone.

Melting range, page 814—Hydroflumethiazide melts between 270° and 275°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Hydroflumethiazide, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Hydroflumethiazide

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* Patented. See notice, page ii.

Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Hydroflumethiazide in methanol exhibits maxima and minima at the same wavelengths as that of NF Hydroflumethiazide Reference Standard, similarly measured.

pH, page 824—The pH of a 1 in 100 dispersion of Hydroflumethiazide in water is between 4.5 and 7.5.

Water, page 900—Determine the water content of Hydroflumethiazide by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Hydroflumethiazide yields not more than 1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Hydroflumethiazide is 20 parts per million.

Selenium—A *Test preparation* prepared with 200 mg. of Hydroflumethiazide meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Diazotizable substances—

Standard preparation—Weigh accurately 10.0 mg. of NF 2,4-Disulfamyl-5-trifluoromethylaniline Reference Standard, and dissolve in 10 ml. of methanol contained in a 50-ml. volumetric flask. Dilute to volume with methanol, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix.

Test preparation—Weigh accurately 100 mg. of Hydroflumethiazide, transfer to a 50-ml. volumetric flask, and dissolve in 20 ml. methanol. Dilute to volume with methanol, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 50-ml. volumetric flasks. Transfer 5.0 ml. of water to a third 50-ml. volumetric flask to serve as a blank. To each flask add 1 ml. of freshly prepared sodium nitrite solution (1 in 100) and 2 ml. of 1 *N* hydrochloric acid, and allow to stand for 5 minutes. Add 2 ml. of ammonium sulfamate solution (1 in 50), and allow to stand for 5 minutes with frequent swirling. Add 1 ml. of freshly prepared *N*-1-naphthylethylenediamine dihydrochloride solution (1 in 1000). Dilute to volume with water, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at 520 mμ, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance of the solution from the *Test preparation* does not exceed that of the solution from the *Standard preparation*, corresponding to not more than 1 percent of diazotizable substances.

Assay—Transfer to a 100-ml. volumetric flask about 50 mg. of Hydroflumethiazide, accurately weighed, add methanol to volume, and mix. Transfer 2.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Hydroflumethiazide Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 273 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg. of $C_8H_8F_3N_3O_4S_2$ in the Hydroflumethiazide taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Hydroflumethiazide in tight containers.

CATEGORY—Antihypertensive; diuretic.

USUAL DOSE—**50 mg.** to **100 mg.** per day.

USUAL DOSE RANGE—**25 mg.** to **200 mg.**

Hydroflumethiazide Tablets

Hydroflumethiazide Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_8F_3N_3O_4S_2$.

Identification—The solution prepared for measurement of absorbance in the *Assay* exhibits a maximum at 273 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Hydroflumethiazide Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Hydroflumethiazide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer one tablet to a 100-ml. volumetric flask, add 50 ml. of methanol, and shake the flask until the tablet is completely disintegrated. Dilute to volume with methanol, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate with methanol to provide a solution containing approximately 10 mcg. of hydroflumethiazide per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Hydroflumethiazide Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 273 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_8H_8F_3N_3O_4S_2$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of hydroflumethiazide in the tablet; D is the exact concentration, in mcg. per ml., of hydroflumethiazide in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—

Standard preparation—Transfer about 30 mg. of NF Hydroflumethiazide Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add sodium hydroxide solution (1 in 100) to volume, and mix. Transfer 5.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with sodium hydroxide solution (1 in 100), and mix.

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 250-mm. test tube to which is fused a 5-cm. length of 7-mm. tubing) with the aid of a tamping rod about 45 cm. in length and having a disk with a diameter about 1-mm. less than that of the tube. To 1 g. of purified siliceous earth in a 100-ml. beaker add 1 ml. of sodium hydroxide solution (1 in 100), and mix until a uniform, fluffy mixture is obtained. Transfer to the tube, and tamp gently to compress the mixture to a uniform mass.

Assay preparation—Weigh and finely powder not less than 20 Hydroflumethiazide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 75 mg. of hydroflumethiazide, to a 50-ml. volumetric flask, add about 35 ml. of sodium hydroxide solution (1 in 100), shake vigorously, dilute to volume with sodium hydroxide solution (1 in 100), and mix. Transfer 2.0 ml. of this solution to a beaker, and mix with 3 g. of purified siliceous earth until a uniform, fluffy mixture is obtained. Transfer to the prepared chromatographic column, and tamp gently to compress. Scrub the beaker with 1 g. of purified siliceous earth mixed with 1 drop of water, transfer to the column, and tamp gently. Wash the column with 50 ml. of water-saturated chloroform, followed by 50 ml. of water-saturated ether, and discard the eluates. Elute the hydroflumethiazide from the column with 100 ml. of a 1 in 1000 solution of glacial acetic acid in ether, collecting the eluate in a 250-ml. separator. Add 60 ml. of isooctane to the separator, mix, and extract the resulting solution with three 50-ml. portions of sodium hydroxide solution (1 in 100), collecting the extracts in a 200-ml. volumetric flask. Dilute to volume with sodium hydroxide solution (1 in 100), and mix.

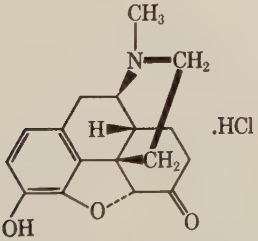
Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 273 mμ, with a suitable spectrophotometer, using sodium hydroxide solution (1 in 100) as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_8H_8F_3N_3O_4S_2$ in the portion of Tablets taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Hydroflumethiazide Tablets in tight containers.

Tablets available—Hydroflumethiazide Tablets usually available contain the following amount of hydroflumethiazide: 50 mg.

CATEGORY and DOSE—See Hydroflumethiazide.

Hydromorphone Hydrochloride



4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one Hydrochloride

$C_{17}H_{19}NO_3 . HCl$ Mol. wt. 321.81

Hydromorphone Hydrochloride, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_{17}H_{19}NO_3.HCl$.

Description—Hydromorphone Hydrochloride occurs as a fine, white or practically white, odorless, crystalline powder. It is affected by light.

Solubility—Hydromorphone Hydrochloride is freely soluble in water. Hydromorphone Hydrochloride is sparingly soluble in alcohol, and is practically insoluble in ether.

Identification—

A: Dissolve about 250 mg. of Hydromorphone Hydrochloride in 25 ml. of water, and add enough ammonia T.S. to render the solution distinctly alkaline. Transfer to a separator, and extract the base with 25 ml. of chloroform. Collect approximately 20 ml. of the chloroform solution and evaporate to dryness on a steam bath. Dry the residue at 105° for 2 hours: the hydromorphone so obtained melts with decomposition at about 260°, *Class Ia*, page 815.

B: A solution of Hydromorphone Hydrochloride (1 in 20) responds to the tests for *Chloride*, page 808.

C: Dissolve 10 mg. of Hydromorphone Hydrochloride in 1 ml. of water, and add a mixture of 5 ml. of potassium ferricyanide T.S. and 5 drops of ferric chloride T.S.: a deep blue color is produced at once.

Specific rotation, page 822—The specific rotation of Hydromorphone Hydrochloride, calculated on the dried basis, determined in a solution containing 200 mg. of Hydromorphone Hydrochloride in each 10 ml., is between −136° and −139°.

Acidity—Dissolve 300 mg. of Hydromorphone Hydrochloride in 10 ml. of water, add 1 drop of methyl red T.S., and titrate with 0.02 *N* sodium hydroxide: not more than 0.3 ml. is required to produce a yellow color.

Loss on drying, page 814—Dry Hydromorphone Hydrochloride at 105° for 2 hours: it loses not more than 1.5 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 200 mg. of Hydromorphone Hydrochloride is negligible.

Sulfate—To a solution of 100 mg. of Hydromorphone Hydrochloride in 5 ml. of water add 0.5 ml. of diluted hydrochloric acid and 1 ml. of barium chloride T.S.: no turbidity is produced.

Codeine—Dissolve 20 mg. of Hydromorphone Hydrochloride in 5 ml. of sulfuric acid, add 1 drop of ferric chloride T.S. and heat in a boiling water bath for 2 minutes: no blue color results.

Assay—Weigh accurately about 225 mg. of Hydromorphone Hydrochloride, previously dried at 105° for 2 hours, transfer to a 250-ml. conical flask, and dissolve in 80 ml. of glacial acetic acid, warming if necessary. Cool, and add 5 ml. of acetic anhydride and 10 ml. of mercuric acetate T.S. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 32.18 mg. of $C_{17}H_{19}NO_3.HCl$.

Packaging and storage—Preserve Hydromorphone Hydrochloride in tight, light-resistant containers.

CATEGORY—Analgesic (narcotic).

USUAL DOSE—Oral and subcutaneous, **2 mg.** every 4 hours as necessary.

USUAL DOSE RANGE—**1** to **4 mg.**

Hydromorphone Hydrochloride Injection

Hydromorphone Hydrochloride Injection is a sterile solution of hydromorphone hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{17}H_{19}NO_3.HCl$.

Identification—From a volume of Hydromorphone Hydrochloride Injection, equivalent to about 50 mg. of hydromorphone hydrochloride, extract the base as described in *Identification test A* under *Hydromorphone Hydrochloride*, page 353, using proportionate quantities of the reagents: the base so obtained melts with decomposition at about 260°, page 814. A 10-mg. portion of the base dissolved in a mixture of 1 drop of diluted hydrochloric acid and 1 ml. of water responds to *Identification test C* under *Hydromorphone Hydrochloride*, page 353.

pH, page 824—The pH of Hydromorphone Hydrochloride Injection is between 4.0 and 5.5.

Other requirements—Hydromorphone

Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—

Standard preparation—Weigh accurately about 50 mg. of NF Hydromorphone Hydrochloride, previously dried at 105° for 2 hours, and dissolve in sufficient water to make 50.0 ml.

Assay preparation—Transfer an accurately measured volume of Hydromorphone Hydrochloride Injection, equivalent to about 24 mg. of hydromorphone hydrochloride, to a 25-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Transfer 6.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 50-ml. volumetric flasks. To each flask add, with mixing, 10 ml. of 1 *N* hydrochloric acid and 1.0 ml. of freshly prepared sodium nitrite solution (1 in 20). Stopper the flasks, allow to stand for 15 to 20 minutes, then add 2 ml. of stronger ammonia T.S., and mix. Dilute to volume with water, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 440 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{17}H_{19}NO_3 . HCl$ in each ml. of the Injection taken by the formula $0.025 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Hydromorphone Hydrochloride Injection in single-dose or in multiple-dose containers, of Type I glass, protected from light.

Injections available—Hydromorphone Hydrochloride Injection usually available contains the following amounts of hydromorphone hydrochloride: 1, 2, 3, and 4 mg. in 1 ml.; 20 mg. in 10 ml.; 40 mg. in 20 ml.

CATEGORY and DOSE—See Hydromorphone Hydrochloride.

Hydromorphone Hydrochloride Tablets

Hydromorphone Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{19}NO_3 . HCl$.

Identification—Dissolve a quantity of Hydromorphone Hydrochloride Tablets, equivalent to about 50 mg. of hydromorphone hydrochloride, in 10 ml. of water, and filter if necessary. Extract the base as described in *Identification test A* under *Hydromorphone Hydrochloride*, page 353. The base so obtained melts with decomposition at about 260°, page 814. A 10-mg. portion of the base, dissolved in a mixture of 1 drop of diluted hydrochloric acid and 1 ml. of water, responds to *Identification test C* under *Hydromorphone Hydrochloride*, page 353.

Disintegration, page 878—The disintegration time limit for Hydromorphone Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Hydromorphone Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Hydromorphone Hydrochloride Injection*, page 354.

Assay preparation—Weigh and finely powder not less than 20 Hydromorphone Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of hydromorphone hydrochloride, to a 50-ml. volumetric flask, add water to volume, mix, and filter.

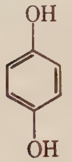
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Hydromorphone Hydrochloride Injection*, page 354. Calculate the quantity, in mg., of $C_{17}H_{19}NO_3 . HCl$ in the portion of the Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Hydromorphone Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Hydromorphone Hydrochloride Tablets usually available contain the following amounts of hydromorphone hydrochloride: 1, 2, 3, and 4 mg.

CATEGORY and DOSE—See Hydromorphone Hydrochloride.

Hydroquinone



$C_6H_6O_2$ Mol. wt. 110.11

Hydroquinone, dried at 105° for 3 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_6H_6O_2$.

Description—Hydroquinone occurs as fine white needles. It darkens upon exposure to light and air.

Solubility—Hydroquinone is freely soluble in water, in alcohol, and in ether.

Identification—

A: Prepare a solution of Hydroquinone in methanol containing approximately 1 mg. per ml., and spot 5 µl. of this solution on a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G. Allow the spot to dry, and develop the chromatogram in a solvent system consisting of methanol and chloroform (1:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Heat on a hot plate or under a lamp until spots appear: the R_f value of Hydroquinone is about 0.86.

B: A 1 in 40,000 solution of Hydroquinone in methanol exhibits an absorbance maximum at 293 ± 2 mµ.

Melting range, page 814—Hydroquinone melts between 172° and 174°.

Loss on drying, page 814—Dry Hydroquinone at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Hydroquinone yields not more than 0.5 percent of residue on ignition.

Assay—Dissolve about 250 mg. of Hydroquinone, previously dried at 105° for 3 hours and accurately weighed, in a mixture of 100 ml. of water and 10 ml. of 0.1 *N* sulfuric acid, add 3 drops of diphenylamine T.S., and titrate with 0.1 *N* ceric sulfate until a red-violet end-point is reached. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* ceric sulfate is equivalent to 5.506 mg. of $C_6H_6O_2$.

Packaging and storage—Preserve Hydroquinone in well-closed, light-resistant containers.

CATEGORY—Depigmenting agent.

FOR EXTERNAL USE—Topically as a 2 percent ointment to the affected area once or twice daily at 12-hour intervals.

Hydroquinone Ointment

Hydroquinone Ointment contains not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_6H_6O_2$.

Identification—Dissolve a portion of Hydroquinone Ointment, equivalent to about 50 mg. of hydroquinone, in sufficient methanol-chloroform solution (1:1) to make 50 ml.: a 5-µl. portion of this solution responds to *Identification test A* under *Hydroquinone,* page 356.

Weight variation, page 901—Hydroquinone Ointment meets the requirements of the weight variation test for ointments.

Assay—Dissolve an accurately weighed portion of Hydroquinone Ointment, equivalent to about 80 mg. of hydroquinone, in a mixture of 100 ml. of water and 10 ml. of 0.1 *N* sulfuric acid, and continue as directed in the *Assay* under *Hydroquinone,* page 356, beginning with "... add 3 drops of diphenylamine T.S. ..."

Packaging and storage—Preserve Hydroquinone Ointment in well-closed, light-resistant containers.

Ointment available—Hydroquinone Ointment usually available contains 2 percent of hydroquinone.

CATEGORY and USE—See Hydroquinone.

Hydroxypropyl Methylcellulose

Hydroxypropyl Methylcellulose is the propylene glycol ether of methylcellulose. The proportions of its hydroxypropyl and methyl groups, which are attached to the anhydroglucose rings of cellulose by ether linkages, may be varied to produce a range of characteristic properties. Hydroxypropyl Methylcellulose, previously dried at 105° for 2 hours, contains not less than 19.0 percent and not more than 30.0 percent of methoxy (—OCH_3), and not less than 3.0 percent and not more than 12.0 percent of hydroxypropoxy (—OC_3H_6OH). The viscosity of a solution containing 2 g. of Hydroxypropyl Methylcellulose in each 100 g. of solution is not less than 80.0 percent and not more than 120.0 percent of that stated on the label for viscosity types of 100 centipoises or less, and not less than 75.0 percent and not more than 140.0 percent of that stated on the label for viscosity types higher than 100 centipoises.

Description—Hydroxypropyl Methylcellulose occurs as a white to slightly off-white, fibrous or granular powder.

Solubility—Hydroxypropyl Methylcellulose swells in water and produces a clear to opalescent, viscous, colloidal solution. It is insoluble in anhydrous alcohol, in ether, and in chloroform.

Identification—

A: To 100 ml. of water add 1 g. of Hydroxypropyl Methylcellulose: it swells and disperses to form a clear to opalescent, mucilaginous solution, depending upon the intrinsic viscosity, which is stable in the presence of most electrolytes.

B: Add 1 g. of Hydroxypropyl Methylcellulose to 100 ml. of boiling water and stir the mixture: a slurry is formed, but the powdered material does not dissolve. Cool the slurry to 20°: the powder dissolves to form a clear or opalescent mucilaginous solution.

C: Pour a few ml. of the solution prepared for *Identification test B* onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results.

Loss on drying, page 814—Dry Hydroxypropyl Methylcellulose at 105° for 2 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Hydroxypropyl Methylcellulose with nominal viscosities of 50 centipoises and greater yields not more than 1.5 percent of residue on ignition. Hydroxypropyl Methylcellulose with nominal viscosities of less than 50 centipoises yields not more than 3 percent of residue on ignition.

Viscosity—Weigh accurately a sample of Hydroxypropyl Methylcellulose, equivalent to 2 g. on the anhydrous basis, transfer to a wide-mouth, 250-ml. centrifuge bottle, and add 98 g. of water, previously heated to 80° to 90°. Mix with a mechanical stirrer for 10 minutes, then place the bottle in an ice bath until solution is complete, adjust the weight of the solution to 100 g., if necessary, and centrifuge the solution to expel any entrapped air. Adjust the temperature of the solution to 20° ± 0.1°, and determine the viscosity in a suitable viscosimeter of the modified Ubbelohde type as directed under *Viscosity—Procedure for Cellulose Derivatives,* page 889.

Assay for hydroxypropoxy groups—Transfer about 50 mg. of Hydroxypropyl Methylcellulose, previously dried at 105° for 2 hours and accurately weighed, into the 100-ml. boiling flask of a hydroxypropoxy apparatus, and proceed as directed under *Hydroxypropoxy Determination,* page 807. Each ml. of 0.02 N sodium hydroxide is equivalent to 1.5 mg. of hydroxypropoxy groups (—OC_3H_6OH).

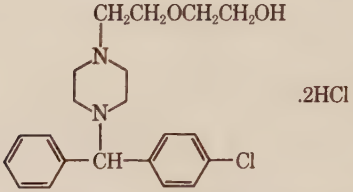
Assay for methoxy groups—Place about 50 mg. of Hydroxypropyl Methylcellulose, previously dried at 105° for 2 hours, in an empty, tared, gelatin capsule, weigh accurately, place the capsule and contents in the boiling flask of a methoxy apparatus, and proceed as directed under *Methoxy Determination,* page 817. Each ml. of 0.1 N sodium thiosulfate is equivalent to 0.5172 mg. of methoxy groups (—OCH_3). Correct the percent of methoxy groups thus determined by the formula $A - (B \times 0.93 \times 31/75)$, in which A is the total —OCH_3 groups determined in the *Assay,* B is the percent of —OC_3H_6OH determined in the *Assay for hydroxypropoxy groups,* and 0.93 is an average obtained by determining, on a large number of samples, the propylene produced from the reaction of hydriodic acid with hydroxypropoxy groups during the assay for methoxy groups. The result represents the actual percent of methoxy groups (—OCH_3) determined in the sample taken for the assay.

Packaging and storage—Preserve Hydroxypropyl Methylcellulose in well-closed containers.

Labeling—Label Hydroxypropyl Methylcellulose to indicate its viscosity type.

CATEGORY—Suspending agent.

Hydroxyzine Hydrochloride*



2-[2-[4-(*p*-Chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]ethanol Dihydrochloride

$C_{21}H_{27}ClN_2O_2 . 2HCl$ Mol. wt. 447.84

Hydroxyzine Hydrochloride, dried at 105° for two hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{21}H_{27}ClN_2O_2 . 2HCl$.

Description—Hydroxyzine Hydrochloride occurs as a white, odorless powder.

Solubility—Hydroxyzine Hydrochloride is soluble in chloroform. It is very soluble in water, slightly soluble in acetone, and practically insoluble in ether.

Identification—To 10 ml. of a solution of Hydroxyzine Hydrochloride (1 in 400) add 2 drops of nitric acid and 1 ml. of silver nitrate T.S.: a curdy, white precipitate, insoluble in diluted nitric acid, but soluble in ammonia T.S., separates (*presence of chloride*).

Melting range, *Class Ia*, page 815—Hydroxyzine Hydrochloride melts with decomposition between 196° and 204°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Hydroxyzine Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Hydroxyzine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Hydroxyzine Hydrochloride in alcohol exhibits maxima and minima at the same wavelengths as that of NF Hydroxyzine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 230 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Hydroxyzine Hydrochloride at 105° for 2 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Hydroxyzine Hydrochloride yields not more than 0.5 percent of residue on ignition. Retain the residue from a 1-g. sample for the *Heavy metals test*.

Heavy metals, page 806—Dissolve the residue resulting from *Residue on ignition* in 23 ml. of water and add 2 ml. of diluted acetic acid: the heavy metals limit for Hydroxyzine Hydrochloride is 50 parts per million.

Assay—Dissolve about 150 mg. of Hydroxyzine Hydrochloride, previously dried at 105° for 2 hours and accurately weighed, in 10 ml. of chloroform. Add 50 ml. of glacial acetic acid, 5 ml. of mercuric acetate T.S., and 4 drops of quinaldine red T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 22.39 mg. of $C_{21}H_{27}ClN_2O_2 . 2HCl$.

Packaging and storage—Preserve Hydroxyzine Hydrochloride in tight containers.

CATEGORY—Tranquilizer (minor).
USUAL DOSE—**25 mg.** three times a day.
USUAL DOSE RANGE—**25** to **100 mg.**

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* Patented. See notice, page ii.

Hydroxyzine Hydrochloride Injection

Hydroxyzine Hydrochloride Injection is a sterile solution of hydroxyzine hydrochloride in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{27}ClN_2O_2 . 2HCl$.

Identification—Dilute a volume of Hydroxyzine Hydrochloride Injection with 0.1 *N* hydrochloric acid to produce a concentration of about 20 mcg. of hydroxyzine hydrochloride per ml. The ultraviolet absorption spectrum of this solution exhibits maxima and minima at the same wavelengths as that of a 1 in 50,000 solution of NF Hydroxyzine Hydrochloride Reference Standard in 0.1 *N* hydrochloric acid, similarly measured.

pH, page 824—The pH of Hydroxyzine Hydrochloride Injection is between 3.5 and 6.0.

Other requirements—Hydroxyzine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—Transfer an accurately measured volume of Hydroxyzine Hydrochloride Injection, equivalent to about 100 mg. of hydroxyzine hydrochloride, to a 250-ml. separator containing 20 ml. of 0.1 *N* sodium hydroxide, and extract with four 50-ml. portions of chloroform, filtering the extracts through a layer of anhydrous sodium sulfate into a 250-ml. beaker. Evaporate the chloroform to a volume of about 10 ml. on a steam bath with the aid of a stream of nitrogen or air, and cool. Add 10 ml. of glacial acetic acid, 5 ml. of acetic anhydride, 5 ml. of mercuric acetate T.S., and 1 drop of quinaldine red T.S., and titrate with 0.02 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.02 *N* perchloric acid is equivalent to 4.478 mg. of $C_{21}H_{27}ClN_2O_2.2HCl$.

Packaging and storage—Preserve Hydroxyzine Hydrochloride Injection in single-dose or in multiple-dose containers, protected from light.

Injections available—Hydroxyzine Hydrochloride Injection usually available contains the following amounts of hydroxyzine hydrochloride; 25 and 50 mg. in 1 ml.; 100 mg. in 2 ml.; and 250 and 500 mg. in 10 ml.

CATEGORY and DOSE—See Hydroxyzine Hydrochloride.

Hydroxyzine Hydrochloride Syrup

Hydroxyzine Hydrochloride Syrup contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{27}ClN_2O_2.2HCl$.

Identification—Dilute a volume of Hydroxyzine Hydrochloride Syrup, equivalent to about 20 mg. of hydroxyzine hydrochloride, with 25 ml. of 1 *N* sodium hydroxide and 25 ml. of acetone, and mix. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G and dried in air for 30 minutes followed by drying in vacuum at 140° for 30 minutes, spot 10 μl. of this solution and 10 μl. of a solution, in the same medium, containing about 350 mcg. of NF Hydroxyzine Hydrochloride Reference Standard per ml. Allow the spots to dry, and develop the chromatogram with 0.1 *N* hydrochloric acid until the solvent front is about 2.5 cm. from the top of the plate. Remove the plate from the developing chamber, and locate the spots by lightly spraying with potassium iodoplatinate T.S.: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Assay—Transfer an accurately measured volume of Hydroxyzine Hydrochloride Syrup, equivalent to about 40 mg. of hydroxyzine hydrochloride, to a 250-ml. separator containing 20 ml. of 0.1 *N* sodium hydroxide, and extract with three 50-ml. portions of chloroform, filtering the extracts through a layer of anhydrous sodium sulfate into a 250-ml. beaker. Evaporate the chloroform to a volume of about 10 ml. on a steam bath with the aid of a stream of nitrogen or air, and cool. Add 10 ml. of glacial acetic acid, 5 ml. of acetic anhydride, 5 ml. of mercuric acetate T.S., and 1 drop of quinaldine red T.S., and titrate with 0.02 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.02 *N* perchloric acid is equivalent to 4.478 mg. of $C_{21}H_{27}ClN_2O_2.2HCl$.

Packaging and storage—Preserve Hydroxyzine Hydrochloride Syrup in tight, light-resistant containers.

Syrup available—Hydroxyzine Hydrochloride Syrup usually available contains the following amount of hydroxyzine hydrochloride: 10 mg. in 5 ml.

CATEGORY and DOSE—See Hydroxyzine Hydrochloride.

Hydroxyzine Hydrochloride Tablets

Hydroxyzine Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{27}ClN_2O_2.2HCl$.

Identification—Triturate a quantity of finely powdered Hydroxyzine Hydrochloride Tablets, equivalent to about 50 mg. of hydroxyzine hydrochloride, with 20 ml. of chloroform, filter, evaporate the chloroform on a steam bath, and dry at 105° for 30 minutes. The ultraviolet absorption spectrum of a 1 in 100,000 solution of the residue so obtained, in alcohol exhibits maxima and minima at the same wavelengths as that of NF Hydroxyzine Hydrochloride Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Hydroxyzine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Hydroxyzine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer a tablet to a 200-ml. volumetric flask, add 100 ml. of water, and heat on a steam bath with occasional stirring until dispersed. Cool, dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with 0.1 N hydrochloric acid to provide a solution containing approximately 10 mcg. of hydroxyzine hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Hydroxyzine Hydrochloride Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 230 mμ, with a suitable spectrophotometer, using 0.1 N hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{21}H_{27}ClN_2O_2 . 2HCl$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of hydroxyzine hydrochloride, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of hydroxyzine hydrochloride in the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

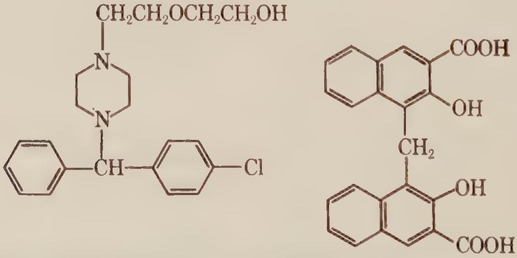
Assay—Triturate 20 Hydroxyzine Hydrochloride Tablets with 25 ml. of chloroform, and quantitatively transfer the supernatant liquid to a 250-ml. glass-stoppered conical flask. Triturate the residue with a second 25-ml. portion of chloroform, and add the supernatant liquid to the flask. Quantitatively transfer the tablet residue to the flask with the aid of 50 ml. of chloroform, and shake mechanically for 30 minutes. Filter the mixture into a 250-ml. volumetric flask, and wash the conical flask with four 25-ml. portions of chloroform, filtering each portion into the volumetric flask. Dilute the combined filtrates to volume with chloroform, and mix. Transfer an accurately measured volume of this solution, equivalent to 150 to 200 mg. of hydroxyzine hydrochloride, to a conical flask, and evaporate on a steam bath to a volume of about 15 ml. with the aid of a current of air. To the residual liquid add 10 ml. of glacial acetic acid, 5 ml. of acetic anhydride, 5 ml. of mercuric acetate T.S., and 3 drops of quinaldine red T.S., and titrate with 0.1 N perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N perchloric acid is equivalent to 22.39 mg. of $C_{21}H_{27}ClN_2O_2 . 2HCl$.

Packaging and storage—Preserve Hydroxyzine Hydrochloride Tablets in tight containers.

Tablets available—Hydroxyzine Hydrochloride Tablets usually available contain the following amounts of hydroxyzine hydrochloride: 10, 25, and 100 mg.

CATEGORY and DOSE—See Hydroxyzine Hydrochloride.

Hydroxyzine Pamoate*



2-[2-[4-(p-Chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]ethanol 4,4′-Methylenebis-[3-hydroxy-2-naphthoate] (1:1)

$C_{21}H_{27}ClN_2O_2 . C_{23}H_{16}O_6$ Mol. wt. 763.29

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* Patented. See notice, page ii.

Hydroxyzine Pamoate contains not less than 97.0 percent and not more than 102.0 percent of $C_{21}H_{27}ClN_2O_2 . C_{23}H_{16}O_6$, calculated on the anhydrous basis.

Description—Hydroxyzine Pamoate occurs as a light yellow, practically odorless powder.

Solubility—Hydroxyzine Pamoate is practically insoluble in water and in methanol. It is freely soluble in dimethylformamide.

Identification—Prepare a solution of Hydroxyzine Pamoate in a mixture of equal volumes of 1 *N* sodium hydroxide and acetone containing 2 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.6-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a solution of NF Hydroxyzine Pamoate Reference Standard in the same medium containing 2 mg. per ml. Allow the spots to dry, and develop the chromatogram in 0.1 *N* hydrochloric acid until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and locate the spots on the plate by viewing under longwave ultraviolet light: the R_f value of the main spot, representing the pamoate moiety, obtained from the sample solution corresponds to that obtained from the Reference Standard solution. Spray the plate lightly with potassium iodoplatinate T.S.: the R_f value of the main spot, representing the hydroxyzine moiety, obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Ultraviolet absorption, page 866—Transfer about 85 mg. of Hydroxyzine Pamoate (equivalent to about 50 mg. of hydroxyzine hydrochloride) to a separator containing 25 ml. of sodium hydroxide T.S., and extract with three 20-ml. portions of chloroform. Evaporate the combined chloroform extracts to dryness on a steam bath with the aid of a current of air, and dissolve the residue in sufficient 0.1 *N* hydrochloric acid to make 100 ml. Dilute a 1-ml. portion of this solution to 50 ml. with 0.1 *N* hydrochloric acid: the ultraviolet absorption spectrum of the solution so obtained exhibits maxima and minima at the same wavelengths as that of a 1 in 100,000 solution of NF Hydroxyzine Hydrochloride Reference Standard in 0.1 *N* hydrochloric acid, similarly measured.

Water, page 900—Determine the water content of Hydroxyzine Pamoate by the titrimetric method: not more than 5 percent is found.

Residue on ignition, page 858—Hydroxyzine Pamoate yields not more than 0.5 percent of residue on ignition. Retain the residue on ignition from a 1-g. sample for the *Heavy metals test.*

Heavy metals, *Method II*, page 806—To the residue obtained in the test for *Residue on ignition* add 1 ml. of hydrochloric acid and 0.5 ml. of nitric acid and evaporate to dryness on a steam bath. Add 2 ml. of diluted acetic acid, digest on the steam bath for 5 minutes, filter, and wash the residue with sufficient water to make 25 ml.: the heavy metals limit for Hydroxyzine Pamoate is 50 parts per million.

Assay—Transfer 600 mg. of Hydroxyzine Pamoate, accurately weighed, to a 125-ml. separator, suspend the sample in 25 ml. of 1 *N* sodium hydroxide, and extract with six 25-ml. portions of chloroform, shaking each extraction for two minutes. After the sixth extraction the aqueous layer should be clear or not more than very slightly turbid. Combine the chloroform extracts, and evaporate to about 20 ml. on a steam bath. Transfer the solution to a 50-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 20.0 ml. of the solution to a 150-ml. beaker, add 50 ml. of glacial acetic acid and 3 drops of quinaldine red T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 38.16 mg. of $C_{21}H_{27}ClN_2O_2 . C_{23}H_{16}O_6$.

Packaging and storage—Preserve Hydroxyzine Pamoate in tight containers.

CATEGORY—Tranquilizer (minor).

USUAL DOSE RANGE—The equivalent of **25 mg.** of hydroxyzine hydrochloride three times a day to the equivalent of **100 mg.** of hydroxyzine hydrochloride four times a day.

Hydroxyzine Pamoate Capsules

Hydroxyzine Pamoate Capsules contain $C_{21}H_{27}ClN_2O_2 . C_{23}H_{16}O_6$ (hydroxyzine pamoate) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{27}ClN_2O_2 . 2HCl$ (hydroxyzine hydrochloride).

Identification—

A: Dissolve a portion of the contents of Hydroxyzine Pamoate Capsules, equivalent to about 100 mg. of hydroxyzine pamoate, in a mixture consisting of 25 ml. of 0.1 *N* sodium hydroxide and 25 ml. of acetone, and filter: a 10-μl. portion of the filtrate meets the requirements of the *Identification test* under *Hydroxyzine Pamoate*, page 360.

B: The ultraviolet absorption spectrum of the solution prepared from Hydroxyzine Pamoate Capsules as directed in the *Assay* exhibits maxima and minima at the same wavelengths as that of a 1 in 100,000 solution of NF Hydroxyzine Hydrochloride Reference Standard in 0.1 *N* hydrochloric acid, similarly measured.

Content uniformity, *Method I*, page 798—Hydroxyzine Pamoate Capsules meet the requirements of the content uniformity test for capsules.

Assay—Transfer as completely as possible the contents of not less than 20 Hydroxyzine Pamoate Capsules to a tared beaker, and determine the average weight per capsule. Mix the combined contents thoroughly, and transfer an accurately weighed portion, equivalent to about 50 mg. of hydroxyzine hydrochloride, to a separator, add 25 ml. of 5 *N* sodium hydroxide, and extract with five 45-ml. portions of chloroform, shaking each portion for 2 minutes. Filter the extracts through anhydrous sodium sulfate into a 250-ml. volumetric flask, dilute to volume with chloroform, and mix. Evaporate a 5.0-ml. portion of this solution to dryness on a steam bath with the aid of a current of air. Dissolve the residue in about 25 ml. of 0.1 *N* hydrochloric acid, transfer the solution to a 100-ml. volumetric flask, rinsing the flask with 0.1 *N* hydrochloric acid, dilute to volume with 0.1 *N* hydrochloric acid, mix, and filter, discarding the first 10-ml. of filtrate. Concomitantly determine the absorbance of the subsequent filtrate and of a solution of NF Hydroxyzine Hydrochloride Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 232 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the equivalent quantity, in mg., of $C_{21}H_{27}ClN_2O_2.2HCl$ in the portion of Capsules taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Hydroxyzine Pamoate Capsules in well-closed containers.

Capsules available—Hydroxyzine Pamoate Capsules usually available contain hydroxyzine pamoate equivalent to the following amounts of hydroxyzine hydrochloride: 25, 50, and 100 mg.

Category and Dose—See Hydroxyzine Pamoate.

Hydroxyzine Pamoate Oral Suspension

Hydroxyzine Pamoate Oral Suspension contains $C_{21}H_{27}ClN_2O_2.C_{23}H_{16}O_6$ (hydroxyzine pamoate) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{27}ClN_2O_2.2HCl$ (hydroxyzine hydrochloride).

Identification—Dissolve a portion of Hydroxyzine Pamoate Oral Suspension, equivalent to about 100 mg. of hydroxyzine pamoate, in a mixture of 25 ml. of 0.1 *N* sodium hydroxide and 25 ml. of acetone, and filter: a 10-μl. portion of the filtrate meets the requirements of the *Identification test* under *Hydroxyzine Pamoate*, page 360.

pH, page 824—The pH of Hydroxyzine Pamoate Oral Suspension is between 4.5 and 7.0.

Assay—Transfer an accurately measured volume of Hydroxyzine Pamoate Oral Suspension, equivalent to about 25 mg. of hydroxyzine hydrochloride, to a 125-ml. separator, add 50 ml. of chloroform, and mix. Add 25 ml. of 5 *N* sodium hydroxide, and shake for 2 minutes. Allow the layers to separate, and filter the chloroform layer through anhydrous sodium sulfate into a 250-ml. volumetric flask. Repeat the extraction with five 25-ml. portions of chloroform, filtering each extract through anhydrous sodium sulfate into the volumetric flask. Wash the sodium sulfate with about 25 ml. of chloroform, dilute the combined chloroform solutions to volume, and mix. Transfer 5.0 ml. of this solution to a 50-ml. volumetric flask, and evaporate to dryness on a steam bath with the aid of a stream of nitrogen. Cool, dissolve the residue in 0.1 *N* hydrochloric acid with gentle warming, dilute to volume with 0.1 *N* hydrochloric acid, mix, and filter, discarding the first 10-ml. of filtrate. Concomitantly determine the absorbance of the subsequent filtrate and of a solution of NF Hydroxyzine Hydrochloride Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about

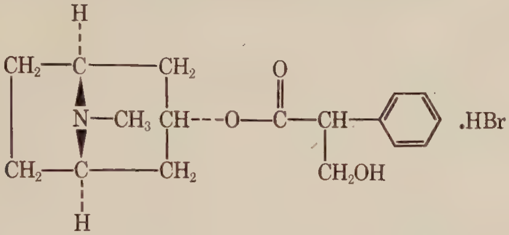
232 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the equivalent quantity, in mg., of $C_{21}H_{27}ClN_2O_2 . 2HCl$ in each ml. of the Suspension taken by the formula $2.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard, V is the volume, in ml., of the Suspension taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Hydroxyzine Pamoate Oral Suspension in tight, light-resistant containers.

Suspension available—Hydroxyzine Pamoate Oral Suspension usually available contains hydroxyzine pamoate equivalent to the following amount of hydroxyzine hydrochloride: 25 mg. in 5 ml.

CATEGORY and DOSE—See Hydroxyzine Pamoate.

Hyoscyamine Hydrobromide



1αH,5αH-Tropan-3α-ol (−)-Tropate (Ester) Hydrobromide

$C_{17}H_{23}NO_3 . HBr$ Mol. wt. 370.29

Hyoscyamine Hydrobromide contains not less than 98.5 percent and not more than 100.5 percent of $C_{17}H_{23}NO_3 . HBr$, calculated on the dried basis.

Caution: Hyoscyamine Hydrobromide is extremely poisonous.

Description—Hyoscyamine Hydrobromide occurs as white, odorless crystals or as a crystalline powder. The pH of a 1 in 20 solution is about 5.4. It is affected by light.

Solubility—Hyoscyamine Hydrobromide is freely soluble in water. It is freely soluble in alcohol and in chloroform. It is very slightly soluble in ether.

Identification—

A: Place about 10 mg. of Hyoscyamine Hydrobromide in a porcelain dish, add 5 drops of nitric acid, evaporate to dryness on a steam bath, and add a few drops of alcoholic potassium hydroxide T.S. to the residue: a violet color is produced.

B: To about 1 ml. of a solution of Hyoscyamine Hydrobromide (1 in 20) add gold chloride T.S., dropwise with shaking, until a definite precipitate separates. Add a small amount of diluted hydrochloric acid, dissolve the precipitate with the aid of heat, and allow the solution to cool: lustrous reddish brown scales that may be accompanied by reddish brown needles are formed (*distinction from atropine and scopolamine*).

C: To an aqueous solution of Hyoscyamine Hydrobromide (1 in 20) add silver nitrate T.S.: a yellowish white precipitate forms which is insoluble in nitric acid.

Melting temperature, page 814—Hyoscyamine Hydrobromide does not melt below 149°.

Loss on drying, page 814—Dry Hyoscyamine Hydrobromide at 105° for 2 hours: it loses not more than 1 percent of its weight.

Specific rotation, page 822—The specific rotation of Hyoscyamine Hydrobromide, previously dried at 105° for 2 hours, determined in a solution in water containing 500 mg. of Hyoscyamine Hydrobromide in each 10 ml., is not less than −24°.

Residue on ignition, page 858—Hyoscyamine Hydrobromide yields not more than 0.2 percent of residue on ignition.

Other alkaloids—Dissolve 250 mg. of Hyoscyamine Hydrobromide in 1 ml. of 0.1 *N* hydrochloric acid and dilute with water to make 15 ml. To 5 ml. of the solution add a few drops of platinic chloride T.S.: no precipitate is formed immediately. To another 5-ml. portion, add 2 ml. of ammonia T.S.: the mixture may develop a slight opalescence, but no turbidity or precipitate is formed immediately.

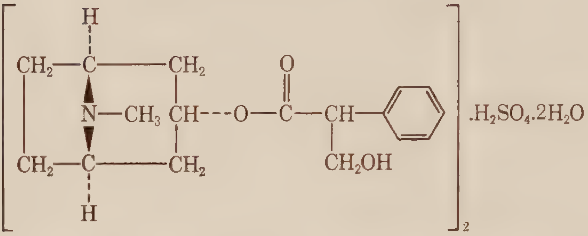
Assay—Dissolve about 700 mg. of Hyoscyamine Hydrobromide, accurately weighed, in a mixture of 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 37.03 mg. of $C_{17}H_{23}NO_3.HBr$.

Packaging and storage—Preserve Hyoscyamine Hydrobromide in tight, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**250 mcg.** to **1.0 mg.**

Hyoscyamine Sulfate



1αH,5αH-Tropan-3α-ol (−)-Tropate (Ester) Sulfate (2:1)

$(C_{17}H_{23}NO_3)_2.H_2SO_4.2H_2O$ Mol. wt. 712.86

Hyoscyamine Sulfate contains not less than 98.5 percent and not more than 100.5 percent of $(C_{17}H_{23}NO_3)_2.H_2SO_4$, calculated on the anhydrous basis.

Caution: Hyoscyamine Sulfate is extremely poisonous.

Description—Hyoscyamine Sulfate occurs as white, odorless crystals or as a crystalline powder. It is deliquescent. It is affected by light. Its solutions are acid to litmus.

Solubility—Hyoscyamine Sulfate is very soluble in water and is freely soluble in alcohol. It is practically insoluble in ether.

Identification—

A: Place about 10 mg. of Hyoscyamine Sulfate in a porcelain dish, add 5 drops of nitric acid, evaporate to dryness on a steam bath, and add a few drops of alcoholic potassium hydroxide T.S. to the residue: a violet color is produced.

B: To about 1 ml. of a solution of Hyoscyamine Sulfate (1 in 20) add gold chloride T.S., dropwise with shaking, until a definite precipitate separates. Add a small amount of diluted hydrochloric acid, dissolve the precipitate with the aid of heat and allow the solution to cool: lustrous golden-yellow scales are formed (*distinction from atropine and scopolamine*).

C: Hyoscyamine Sulfate (1 in 20) responds to the test for *Sulfate*, page 810.

Melting temperature, page 814—Hyoscyamine Sulfate, previously dried at 105° for 4 hours, does not melt below 200°.

Water, page 900—Determine the water content of Hyoscyamine Sulfate by the titrimetric method: not less than 4 percent and not more than 6 percent is found.

Specific rotation, page 822—The specific rotation of Hyoscyamine Sulfate, previously dried at 105° for 4 hours, determined in a solution in water containing 500 mg. of Hyoscyamine Sulfate in each 10 ml., is not less than −24°.

Readily carbonizable substances, page 856—Dissolve 200 mg. of Hyoscyamine Sulfate in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid A.

Residue on ignition, page 858—Hyoscyamine Sulfate yields not more than 0.2 percent of residue on ignition.

Other alkaloids—Dissolve 250 mg. of Hyoscyamine Sulfate in 1 ml. of 0.1 *N* hydrochloric acid and dilute with water to make 15 ml. To 5 ml. of the solution add a few drops of platinic chloride T.S.: no precipitate is formed. To another 5-ml. portion, add 2 ml. of ammonia T.S.: the mixture may develop a slight opalescence, but no turbidity or precipitate is formed immediately.

Assay—Dissolve about 1 g. of Hyoscyamine Sulfate, accurately weighed, in 50 ml. of glacial acetic acid, and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 67.68 mg. of $(C_{17}H_{23}NO_3)_2.H_2SO_4$.

Packaging and storage—Preserve Hyoscyamine Sulfate in tight, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE RANGE—**125** to **250 mcg.** three or four times a day.

Hyoscyamine Sulfate Tablets

Hyoscyamine Sulfate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $(C_{17}H_{23}NO_3)_2 . H_2SO_4 . 2H_2O$.

Identification—Macerate a quantity of powdered Hyoscyamine Sulfate Tablets, equivalent to about 5 mg. of hyoscyamine sulfate, with 20 ml. of water, and transfer to a separator. Make the solution alkaline with ammonia T.S., and extract the alkaloid with 50 ml. of chloroform. Filter the chloroform layer, divide it into two equal portions, and evaporate to dryness. Perform tests *A* and *B* on the residue.

A: To one portion of the dry residue add 2 drops of nitric acid, evaporate to dryness on a steam bath, and add a few drops of alcoholic potassium hydroxide T.S.: a violet color is produced.

B: Dissolve the other portion of the residue in 1 ml. of 0.1 *N* hydrochloric acid, and add gold chloride T.S., dropwise with shaking, until a definite precipitate separates. Slowly heat until the precipitate dissolves, and allow the solution to cool: lustrous golden yellow scales are formed.

Disintegration, page 878—The disintegration time limit for Hyoscyamine Sulfate Tablets is 10 minutes.

Content uniformity, *Method I,* page 799—Hyoscyamine Sulfate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Internal standard solution—Prepare a solution in chloroform containing 100.0 mg. of anthracene in each ml.

Standard preparation—Transfer about 12.5 mg. of NF Hyoscyamine Sulfate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix. Transfer 2.0 ml. of this solution to a 60-ml. separator, and continue as directed under *Assay preparation,* beginning with "... add 20 ml. of water and 5 drops of ammonia T.S. ..."

Assay preparation—Weigh and finely powder not less than 20 Hyoscyamine Sulfate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 250 mcg. of hyoscyamine sulfate, to a 60-ml. separator, add 20 ml. of water and 5 drops of ammonia T.S., and extract with three 25-ml. portions of chloroform, filtering each extract through cotton into a suitable container. Evaporate the combined extracts to a volume of about 5 ml. on a steam bath with the aid of a current of air. With the aid of about 5 ml. of chloroform, transfer the residual liquid to a 10-ml. glass-stoppered conical flask, evaporate to near dryness in the same manner, and then remove the last few ml. of chloroform at reduced pressure. Transfer 2.0 ml. of *Internal standard solution* to the flask, and swirl to dissolve. Use the resultant solution as directed in the *Procedure.*

Procedure—Inject an appropriate volume of the *Standard preparation* into a suitable gas chromatograph equipped with a flame-ionization detector, and record the chromatogram. Under typical conditions, the instrument contains a 1-meter × 6-mm. (outside diameter) glass column packed with 5 percent methyl silicone gum on 80 to 100-mesh or 100 to 120-mesh acid-washed, silanized, flux-calcined siliceous earth. The column is maintained at 200° and the injector port and detector block at 230°; helium is used as the carrier gas at a flow rate of 50 ml. per minute.

Measure the peak height of each component, recording the height of the anthracene peak as P_1 and that of the hyoscyamine peak as P_2.

Similarly, inject an appropriate volume of the *Assay preparation* into the chromatograph, and record the chromatogram under the same conditions as described for the *Standard preparation.* Measure the peak height of each component, recording the height of the anthracene peak as p_1 and that of the hyoscyamine peak as p_2.

Calculate the quantity, in mcg., of $(C_{17}H_{23}NO_3)_2 . H_2SO_4 . 2H_2O$ in the portion of Tablets taken by the formula $C \times (p_2 \times P_1)/(p_1 \times P_2)$, in which C is the exact equivalent concentration, in mcg. per ml., of hyoscyamine sulfate in the *Standard preparation.*

Packaging and storage—Preserve Hyoscyamine Sulfate Tablets in tight, light-resistant containers.

Tablets available—Hyoscyamine Sulfate Tablets usually available contain the following amounts of hyoscyamine sulfate: 125 mcg. and 250 mcg.

CATEGORY and DOSE—See Hyoscyamine Sulfate.

Hypophosphorous Acid

H_3PO_2 Mol. wt. 66.00

Hypophosphorous Acid contains not less than 30.0 percent and not more than 32.0 percent of H_3PO_2.

Description—Hypophosphorous Acid is a colorless or slightly yellow, odorless liquid. Its specific gravity is about 1.13.

Identification—Hypophosphorous Acid responds to the tests for *Hypophosphite,* page 808.

Test liquid—Hypophosphorous Acid, diluted with 3 volumes of water, meets the requirements of the following tests for *Arsenic, Barium,* and *Oxalate.*

Arsenic—Mix 25 ml. of the *Test liquid* with 5 ml. of 30 percent hydrogen peroxide solution, and evaporate to dryness on a steam bath. Cool, add 10 ml. of diluted sulfuric acid, and evaporate to strong fuming of sulfur trioxide, cool, add cautiously 10 ml. of water, and again evaporate to strong fuming, repeating if necessary to remove any trace of hydrogen peroxide. Cool, and dilute cautiously with water to 35 ml. This *Test Preparation* meets the requirements of the *Arsenic Test,* page 777 (1.5 parts per million As).

Barium—Neutralize 30 ml. of the *Test liquid* with ammonia T.S.: the mixture exhibits little or no precipitation. Filter, acidify 10 ml. of the filtrate with hydrochloric acid, and add 2 ml. of potassium sulfate T.S.: no turbidity is produced.

Oxalate—Another 10-ml. portion of the filtrate obtained in the test for *Barium* shows no turbidity upon the addition of 1 ml. of calcium chloride T.S.

Heavy metals, page 806—Place 0.9 ml. (1 g.) of Hypophosphorous Acid in a small beaker, and add 3 ml. of water. Add 1 ml. of nitric acid, and evaporate on a steam bath to about 1 ml. Again add 1 ml. of nitric acid, and evaporate on the steam bath. Dissolve the residue in 3 ml. of water, add ammonia T.S. until the solution is distinctly alkaline to litmus, then boil gently until the odor of ammonia disappears. Add 2 ml. of diluted acetic acid and 15 ml. of warm water, filter, and dilute the filtrate with water to 25 ml.: the heavy metals limit for Hypophosphorous Acid is 20 parts per million.

Assay—Pour about 7 ml. of Hypophosphorous Acid into a tared, glass-stoppered flask, and weigh accurately. Dilute with about 25 ml. of water, add phenolphthalein T.S., and titrate with 1 *N* sodium hydroxide. Each ml. of 1 *N* sodium hydroxide is equivalent to 66.00 mg. of H_3PO_2.

Packaging and storage—Preserve Hypophosphorous Acid in tight containers.

CATEGORY—Antioxidant.

Ichthammol

Ichthammol is obtained by the destructive distillation of certain bituminous schists, sulfonating the distillate, and neutralizing the product with ammonia. Ichthammol yields not less than 2.5 percent of NH_3 (ammonia) and not less than 10.0 percent of total S (sulfur).

Description—Ichthammol is a reddish brown to brownish black, viscous fluid, with a strong, characteristic, empyreumatic odor.

Solubility—Ichthammol is miscible with water, with glycerin, and with fixed oils and fats. It is partially soluble in alcohol and in ether.

Identification—

A: To a solution of Ichthammol (1 in 10) add hydrochloric acid: a dark, resinous precipitate is formed which is insoluble in ether.

B: To a solution of Ichthammol (1 in 10) add sodium hydroxide T.S., and heat to the boiling point: ammonia is evolved.

Loss on drying, page 814—Dry Ichthammol at 80° for 8 hours and continue the drying at 100° to constant weight: it loses not more than 50 percent of its weight.

Residue on ignition, page 858—Ichthammol yields not more than 0.5 percent of residue on ignition.

Limit for ammonium sulfate—Accurately weigh about 1 g. of Ichthammol, transfer to a 100-ml. beaker, and add 25 ml. of alcohol. Stir thoroughly, filter, and wash the filter with a mixture of equal parts of ether and alcohol until the last washing is clear and colorless. Air-dry the filter and residue, and pass 200 ml. of warm water, slightly acidified with hydrochloric acid, through the residue on the filter. Heat the filtrate to boiling, add barium chloride T.S. in excess, and heat for 30 minutes on a steam bath. Collect the precipitate of barium sulfate on a filter, wash it well, dry, and ignite to constant weight. Each g. of barium sulfate is equivalent to 566.1 mg. of $(NH_4)_2SO_4$. Ichthammol contains not more than 8 percent of ammonium sulfate.

Assay for ammonia—Dissolve about 5 g. of Ichthammol, accurately weighed, in 100 ml. of water, transfer the solution to a distillation flask, add 1 ml. of octyl alcohol and 20 ml. of sodium hydroxide solution (1 in 2.5). Connect the flask to a condenser by means of a spray trap and immerse the lower outlet tube of the condenser in 30.0 ml. of 0.5 *N* sulfuric acid. Distil slowly and collect about 50 ml. of distillate, then titrate the excess acid with 0.5 *N* sodium hydroxide, using methyl red T.S. as the indicator. Each ml. of 0.5 *N* sulfuric acid is equivalent to 8.515 mg. of NH_3.

Assay for total sulfur—Transfer from 500 to 800 mg. of Ichthammol, accurately weighed, into a Kjeldahl flask with the aid of 20 ml. of water. Add 3 g. of potassium chlorate, then add slowly 30 ml. of nitric acid, and evaporate the mixture on a hot plate to about 5 ml. Repeat the oxidation with 3 g. of potassium chlorate and 30 ml. of nitric acid, and evaporate to about 5 ml. Add 25 ml. of hydrochloric acid and again evaporate to about 5 ml. Add 100 ml. of water, heat to boiling, filter, and wash well. To the hot filtrate add 25 ml. of barium chloride T.S., and heat on a steam bath for 1 hour. Collect the barium sulfate on a previously ignited and tared filter crucible, wash, dry, and ignite, then cool, and weigh. Each g. of barium sulfate is equivalent to 137.4 mg. of S.

Packaging and storage—Preserve Ichthammol in well-closed containers.

CATEGORY—Local anti-infective.

FOR EXTERNAL USE—Topically as a 10 percent ointment.

Ichthammol Ointment

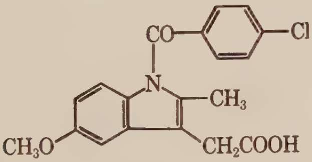
Ichthammol	**100 g.**
Anhydrous Lanolin	**100 g.**
Petrolatum	**800 g.**
To make	**1000 g.**

Thoroughly incorporate the ichthammol with the anhydrous lanolin and then combine this mixture with the petrolatum.

Packaging and storage—Preserve Ichthammol Ointment in tight containers and avoid prolonged exposure to temperatures above 30°.

CATEGORY—See Ichthammol.

Indomethacin*



1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic Acid

$C_{19}H_{16}ClNO_4$ Mol. wt. 357.80

Indomethacin contains not less than 98.0 percent and not more than 101.0 percent of $C_{19}H_{16}ClNO_4$, calculated on the dried basis.

Description—Indomethacin occurs as a pale yellow to a yellow-tan, crystalline powder. It is odorless or has a slight odor. It is sensitive to light. It exhibits polymorphism, one form melting at about 155° and the other at about 162°. It may occur as a mixture of both forms, which mixture may melt within the range of about 155° to 162°.

Solubility—Indomethacin is practically insoluble in water. It is sparingly soluble in alcohol, in chloroform, and in ether.

Identification—

A: Dissolve 300 mg. of Indomethacin in 15 ml. of methanol. To a 5-ml. portion of this solution add one pellet of sodium hydroxide, shake to dissolve, and allow to stand for 5 minutes: the color of the solution changes from a strong yellow through greenish yellow and colorless, to a very light yellow. To another 5-ml. portion add 2.5 ml. of hydrochloric acid: a heavy white precipitate forms, and the supernatant liquid is decolorized to a very light yellow.

B: Dissolve 100 mg. of Indomethacin in 100 ml. of water containing 0.5 ml. of sodium hydroxide T.S. To a 1-ml. portion add 1 ml. of freshly prepared sodium nitrite solution (1 in 1000), allow to stand for about 5 minutes, and add 0.5 ml. of sulfuric acid: a golden yellow color appears. To another 1-ml. portion add 1 ml. of the sodium nitrite solution, allow to stand for about 5 minutes, and add 0.5 ml. of hydrochloric acid: a green color appears.

Infrared absorption, page 866—The

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* Patented. See notice, page ii.

infrared absorption spectrum of a mineral oil dispersion of Indomethacin, previously dried at 100° for 2 hours at a pressure below 5 mm. of mercury, exhibits maxima only at the same wavelengths as that of NF Indomethacin Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 40,000 solution of Indomethacin in 0.1 *N* methanolic hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Indomethacin Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 318 mμ, do not differ by more than 3 percent.

X-ray diffraction, page 902—The X-ray diffraction pattern of Indomethacin conforms to the following pattern:

d	I/I_1
8.70	30
7.60	100
6.96	19
5.31	80
5.21	40
5.12	45
4.77	19
4.58	26
4.52	58
4.34	15
4.25	9
4.06	100
3.88	24
3.83	21
3.70	21
3.48	14
3.39	17
3.34	65
3.31	19
3.24	13
3.15	11
3.10	9
3.04	24
2.93	17
2.73	9
2.62	9
2.39	14

Loss on drying, page 814—Dry Indomethacin at 100° for 2 hours at a pressure below 5 mm. of mercury: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Indomethacin yields not more than 0.2 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Indomethacin is 20 parts per million.

Alkaline hydrolysis—Transfer about 450 mg. of Indomethacin, accurately weighed, to a glass-stoppered conical flask, and dissolve in 25.0 ml. of carbon dioxide-free methanol. While flushing the flask with a stream of carbon dioxide-free nitrogen, add 5.0 ml. of carbon dioxide-free 1 *N* sodium hydroxide, mix, and stopper immediately. Allow to stand for 15 minutes, again flush the flask with carbon dioxide-free nitrogen, add 30 ml. of carbon dioxide-free water, and mix. Restopper immediately, and allow to stand for 90 minutes. Wash the stopper and sides of the flask with 50 ml. of carbon dioxide-free water, add 3 drops of phenolphthalein T.S., and, with continuous nitrogen flush, titrate the excess alkali with 0.1 *N* hydrochloric acid. Determine the normality, N_3, of the 0.1 *N* hydrochloric acid under the conditions of the test by taking an accurately measured volume (3.0 ml.) of the 1 *N* sodium hydroxide, adding 25.0 ml. of carbon dioxide-free methanol, and proceeding as directed for the sample, beginning with "While flushing the flask ..." Calculate the quantity, in mg., of sodium hydroxide required to hydrolyze 1 g. of the sample by the formula $[40(5N_2 - V_4N_3)/W_2] - [40(V_1 - V_2)(N_1)/W_1]$, in which N_1 is the exact normality, and V_1 the volume, in ml., of the 0.1 *N* sodium hydroxide used in the *Assay;* N_2 is the exact normality of the 1 *N* sodium hydroxide used in the alkaline hydrolysis procedure; V_2 is the volume, in ml., of the 0.1 *N* sodium hydroxide used to titrate the blank in the *Assay;* N_3 is the exact normality, and V_4 is the volume, in ml., of the 0.1 *N* hydrochloric acid used to titrate the sample in the alkaline hydrolysis procedure; W_1 is the weight of the *Assay* sample, in g., calculated on the dried basis; and W_2 is the weight of the alkaline hydrolysis sample, in g., calculated on the dried basis: not less than 109 mg. and not more than 113 mg. of sodium hydroxide is required to hydrolyze each g. of Indomethacin, calculated on the dried basis.

Assay—Transfer about 450 mg. of Indomethacin, accurately weighed, to a 250-ml. conical flask, add 75 ml. of methanol which has been purged with carbon dioxide-free nitrogen for 15 minutes, and stir magnetically until the sample has dissolved. Flush out the air above the solution with carbon dioxide-free nitrogen. With continued nitrogen flush, add 75 ml. of carbon dioxide-free water and 0.2 ml. of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 35.78 mg. of $C_{19}H_{16}ClNO_4$.

Packaging and storage—Preserve Indomethacin in well-closed, light-resistant containers.

Category—Anti-inflammatory (nonsteroid).

Usual dose range—**25** or **50 mg.** two or three times a day.

Indomethacin Capsules

Indomethacin Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{19}H_{16}ClNO_4$.

Identification—Transfer the contents of Indomethacin Capsules, equivalent to about 100 mg. of indomethacin, to a test tube containing 15 ml. of methanol, agitate for a few minutes, and then centrifuge: the supernatant liquid responds to *Identification tests A* and *B* under *Indomethacin*, page 367.

Content uniformity, *Method I*, page 798—Indomethacin Capsules meet the requirements of the content uniformity test for capsules.

Dissolution, *Method II*, page 802—Accurately weigh 10 Indomethacin Capsules, and determine the average weight per Capsule. Accurately weigh one of the Capsules, place it in one of the tubes of the basket rack assembly (modified by placing a 10-mesh stainless steel cloth on top of the basket to prevent the capsules from floating out of the tube), and operate the apparatus, using a mixture of 150 ml. of pH 7.2 phosphate buffer solution (page 784) and 600 ml. of water as the *Dissolution Fluid*, contained in a 1000-ml. beaker 14.5 cm. in height and 10 cm. inside diameter. Determine the amount of $C_{19}H_{16}ClNO_4$ in solution after the apparatus has operated for 15 minutes by determining the ultraviolet absorption of filtered aliquots removed from the dissolution solution, diluted with the *Dissolution Fluid* to a concentration of about 30 mcg. of indomethacin per ml., at the maximum at about 318 mμ, in 1-cm. cells, with a suitable spectrophotometer, using the *Dissolution Fluid* as the blank, and utilizing a standard curve, representing absorbance *versus* concentration of NF Indomethacin Reference Standard, similarly measured. Calculate the percent of the labeled amount of $C_{19}H_{16}ClNO_4$ in the Capsule dissolved after 15 minutes, adjusted for weight variation. Repeat the test on 5 more Capsules, tested individually. The requirements are met if the average of the 6 Capsules is not less than 80 percent of the labeled amount. If the average is less than 80 percent, repeat the test on an additional 12 Capsules, tested individually. The requirements are met if the average of the 18 determinations is not less than 80 percent, and if not more than 5 of the 18 results are below 80 percent.

Assay—

Standard preparation—Transfer about 25 mg. of NF Indomethacin Reference Standard, accurately weighed, to a 200-ml. volumetric flask, dissolve in 2 ml. of methanol, dilute to volume with pH 7.2 phosphate buffer, page 784, and mix. Transfer 25.0 ml. of this solution to a separator, and extract with three 25-ml. portions of methylene chloride. Filter the extracts through a pledget of cotton into a 100-ml. volumetric flask, rinse the filter with methylene chloride, dilute to volume with methylene chloride, and mix.

Assay preparation—Transfer as completely as possible the contents of not less than 20 Indomethacin Capsules to a suitable tared container, and determine the average content weight per capsule. Mix the combined contents thoroughly, and transfer an accurately weighed portion, equivalent to about 25 mg. of indomethacin, to a 200-ml. volumetric flask, add 2 ml. of methanol, shake for 10 minutes, dilute to volume with pH 7.2 phosphate buffer, and mix. Transfer about 50 ml. to a centrifuge tube, and centrifuge for 15 minutes. Transfer 25.0 ml. of the supernatant liquid to a 125-ml. separator and extract with three 25-ml. portions of methylene chloride. Filter the extracts through a pledget of cotton into a 100-ml. volumetric flask, rinse the filter with methylene chloride, dilute to volume with methylene chloride, and mix.

Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 318 mμ, with a suitable spectrophotometer, using methylene chloride as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{19}H_{16}ClNO_4$ in the portion of Capsules taken by the formula $0.8C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Indomethacin Capsules in well-closed containers.

Capsules available—Indomethacin Capsules usually available contain the following amounts of indomethacin: 25 mg. and 50 mg.

Category and Dose—See Indomethacin.

Iodine Ampuls

Iodine Ampuls contain, in each 100 ml., not less than 1.8 g. and not more than 2.2 g. of I, and not less than 2.1 g. and not more than 2.6 g. of NaI.

NOTE: Iodine Ampuls contain Iodine Tincture USP.

Assay—Proceed as directed in the *Assay* under *Iodine Solution*, page 370.

Alcohol content, page 772—Iodine Ampuls contain from 44 to 50 percent (v/v) of C_2H_5OH.

CATEGORY—Local anti-infective.

Iodine Solution

Iodine Solution contains, in each 100 ml., not less than 1.8 g. and not more than 2.2 g. of I, and not less than 2.1 g. and not more than 2.6 g. of NaI.

Iodine	**20 g.**
Sodium Iodide	**24 g.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Dissolve the iodine and sodium iodide in 50 ml. of purified water, then add sufficient purified water to make the product measure 1000 ml.

Description—Iodine Solution is a transparent liquid, having a reddish brown color and the odor of iodine.

Identification—Add 1 drop of Iodine Solution to a mixture of 1 ml. of starch T.S. and 9 ml. of water: a deep blue color is produced.

Assay—Pipet 5.0 ml. of Iodine Solution into a 500-ml. glass-stoppered flask, and dilute with 10 ml. of water. Titrate with 0.1 *N* potassium arsenite, using starch T.S. as the indicator. Each ml. of 0.1 *N* potassium arsenite is equivalent to 12.69 mg. of I. To the titration mixture add 25 ml. of hydrochloric acid and 5 ml. of chloroform, and cool to room temperature. Titrate with 0.05 *M* potassium iodate until the purple color of iodine disappears from the chloroform. The last portion of iodate solution must be added dropwise, the mixture being agitated vigorously and continuously. After the chloroform has been decolorized, allow the mixture to stand for 5 minutes. If the chloroform develops a purple color, the mixture should be titrated further with the iodate solution. The difference between the number of ml. of 0.05 *M* potassium iodate used and the number of ml. of 0.1 *N* potassium arsenite used, multiplied by 14.99, equals the number of mg. of NaI in the volume of Solution taken for the assay.

Packaging and storage—Preserve Iodine Solution in tight, light-resistant containers, preferably at a temperature not above 35°.

CATEGORY—Local anti-infective.

Iodized Oil

Iodized Oil is an iodine addition product of vegetable oil or oils, containing not less than 38.0 percent and not more than 42.0 percent of organically combined I (iodine). It is sterile.

Description—Iodized Oil is a thick, viscous, oily liquid, having an alliaceous odor, and an oleaginous taste. Iodized Oil decomposes on exposure to air and sunlight, becoming dark brown in color.

Solubility—Mix 1 ml. of Iodized Oil with 10 ml. of solvent hexane: a clear solution results.

Identification—Mix 0.2 ml. of Iodized Oil with 1 g. of anhydrous sodium carbonate in a small porcelain crucible, cover with 1 g. of anhydrous sodium carbonate, well pressed down, and heat the crucible rapidly and strongly for 10 minutes. Allow the crucible and contents to cool, and dissolve the residue in 20 ml. of hot water. Filter the solution, and add hydrochloric acid cautiously until effervescence ceases. Place 10 ml. of the solution in a test tube, add 2 ml. of chloroform and a few drops of chlorine T.S., and mix: a violet color is produced in the chloroform layer.

Acidity—Dissolve 1 ml. of Iodized Oil in 10 ml. of chloroform in a glass-stoppered cylinder, add 3 drops of phenolphthalein T.S. and 0.3 ml. of 0.1 *N* sodium hydroxide, stopper, and shake the mixture vigorously: a red color is produced.

Residue on ignition, page 858—Iodized Oil yields not more than 0.1 percent of residue on ignition.

Sterility—Iodized Oil meets the requirements under *Sterility Tests*, page 874.

Assay—Weigh accurately about 18 mg. of Iodized Oil in a tared methylcellulose capsule, and proceed as directed under *Oxygen Flask Combustion*, page 823, beginning with "Place the sample, together with a paper fuse-strip . . . ," and using a mixture of 10 ml. of sodium hydroxide solution (1 in 100) and 1 ml. of freshly prepared sodium bisulfite solution (1 in 100) as the absorbing liquid. Following combustion, pipet 1.0 ml. of bromine-sodium acetate T.S. into the cup of the flask, loosen the stopper and allow the solution to be sucked into the flask. Wash down the cup and the ground joint with water, stopper the flask and shake it vigorously, then add 5 drops of formic acid, and again shake the flask. Remove the stopper, and rinse the stopper and sample holder with water, collecting the rinsings in the flask. Bubble nitrogen through the solution to displace all the oxygen from the solution and the flask. Add 500 mg. of potassium iodide and 3 ml. of diluted sulfuric acid, allow the mixture to stand for 2 minutes, and titrate the liberated iodine with 0.05 *N* sodium thiosulfate, adding starch T.S. as the indicator. Each ml. of 0.05 *N* sodium thiosulfate is equivalent to 1.058 mg. of iodine (I).

Packaging and storage—Preserve Iodized Oil in well-filled, single-dose or multiple-dose, light-resistant containers.

CATEGORY—Diagnostic aid (radiopaque—hysterosalpingographic).

USUAL DOSE RANGE—**1** to **30 ml.** by special injection, and depending on procedure.

Iodochlorhydroxyquin and Hydrocortisone Cream

Iodochlorhydroxyquin and Hydrocortisone Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of C_9H_5ClINO (iodochlorhydroxyquin) and of $C_{21}H_{30}O_5$ (hydrocortisone).

Identification—

A: The infrared absorption spectrum of the *Assay preparation*, prepared as directed in the *Assay for iodochlorhydroxyquin*, determined in a 3-mm. cell, exhibits maxima in the region from 7 μ to 11 μ only at the same wavelengths as that of the *Standard preparation*, prepared as directed in the *Assay*, similarly measured.

B: Evaporate 50 ml. of the *Assay preparation*, prepared as directed in the *Assay for hydrocortisone*, just to dryness on a steam bath, and dissolve the residue in 0.5 ml. of a 1:1 mixture of chloroform and methanol. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 10 μl. of this solution and 10 μl. of a 1:1 chloroform-methanol solution of USP Hydrocortisone Reference Standard containing 10 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and methanol (9:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, and allow the solvent to evaporate. Observe under shortwave ultraviolet light, and mark the location of the spots. Spray the plate with a reagent prepared by cautiously dissolving 0.8 ml. of formaldehyde in 10 ml. of sulfuric acid and then adding 3 ml. of water, and heat the plate for 10 minutes at 80°: the R_f value of the main spot from the sample corresponds to that obtained from the Reference Standard solution.

Weight variation, page 901—Iodochlorhydroxyquin and Hydrocortisone Cream meets the requirements of the weight variation test for creams.

Assay for iodochlorhydroxyquin—

NOTE—All glassware should be free from metal contamination.

Standard preparation—Dissolve an accurately weighed amount of USP Iodochlorhydroxyquin Reference Standard, previously dried over phosphorus pentoxide for 5 hours, in sufficient carbon disulfide to obtain a solution containing about 3 mg. per ml.

Assay preparation—Transfer an accurately weighed portion of Iodochlorhydroxyquin and Hydrocortisone Cream, equivalent to about 30 mg. of iodochlorhydroxyquin, to a centrifuge tube, suspend in 10 ml. of carbon tetrachloride by shaking, add 3 ml. of water, and shake for 2 minutes. Centrifuge, and filter the carbon tetrachloride layer through a pledget of cotton into a second centrifuge tube. Repeat the extraction with one 10-ml. and one 5-ml. portion of carbon tetrachloride, and evaporate the combined extracts to about 2 ml. Retain the aqueous phase and the cotton pledget for the *Assay for hydrocortisone.* Extract the residual carbon tetrachloride solution with one 10-ml. followed by three 5-ml. portions of 3.5 *M* hydrochloric acid, filtering each extract through cotton into a 125-ml. separator. To the combined extracts add 3.5 *M* sodium hydroxide, with cooling, until the pH of the solution is between 1 and 2, and then extract with two 5-ml. portions of carbon disulfide. Filter the carbon disulfide phase through cotton into a 10-ml. volumetric flask, dilute to volume with carbon disulfide, and mix. Retain the acid phase for the *Assay for hydrocortisone.*

Procedure—Concomitantly determine the absorbances of the solutions in 3-mm. cells at the maximum of about 14.4 μ and at the minimum at about 14.9 μ, with a suitable infrared spectrophotometer, using carbon disulfide as the blank. Record the absorbances of the *Standard preparation* at 14.4 μ and 14.9 μ as $A_{S14.4}$ and $A_{S14.9}$, respectively, and the absorbances of the *Assay preparation* at 14.4 μ and 14.9 μ as $A_{U14.4}$ and $A_{U14.9}$, respectively. Calculate the quantity, in mg., of C_9H_5ClINO in the portion of the Cream taken by the formula $10C \times (A_{U14.4} - A_{U14.9})/(A_{S14.4} - A_{S14.9})$, in which C is the exact concentration of the *Standard preparation*, in mg. per ml.

Assay for hydrocortisone—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using USP Hydrocortisone Reference Standard.

Assay preparation—With the aid of alcohol, quantitatively transfer the aqueous phase, reserved in the *Assay for iodochlorhydroxyquin*, to a 100-ml. volumetric flask, filtering it through the pledget of cotton reserved in the *Assay* for *iodochlorhydroxyquin*. Extract the acid phase, also reserved in the *Assay for iodochlorhydroxyquin*, with three 10-ml. portions of chloroform, and filter each extract through a pledget of cotton. Evaporate the combined chloroform extracts to dryness on a steam bath, and quantitatively transfer the residue, dissolved in alcohol, to the volumetric flask containing the aqueous phase. Dilute to volume with alcohol, and mix. Transfer an accurately measured volume, V, in ml., of this solution, equivalent to about 1 mg. of hydrocortisone, to a second 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Transfer 20.0 ml. of this final solution to a glass-stoppered, 50-ml. conical flask.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{21}H_{30}O_5$ in the portion of Cream taken by the formula $10 \times (C/V) \times (A_U/A_S)$, in which V is as defined under *Assay preparation*.

Packaging and storage—Preserve Iodochlorhydroxyquin and Hydrocortisone Cream in well-closed containers.

Creams available—Iodochlorhydroxyquin and Hydrocortisone Cream usually available contains 3 percent of iodochlorhydroxyquin and 0.5 percent or 1 percent of hydrocortisone.

CATEGORY—Local anti-infective; glucocorticoid.

APPLICATION—Topically to affected area 3 or 4 times daily as a cream containing 3 percent iodochlorhydroxyquin and 0.5 or 1 percent hydrocortisone.

Iodochlorhydroxyquin and Hydrocortisone Lotion

Iodochlorhydroxyquin and Hydrocortisone Lotion contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of C_9H_5ClINO (iodochlorhydroxyquin) and of $C_{21}H_{30}O_5$ (hydrocortisone).

Identification—

A: The infrared absorption spectrum of the *Assay preparation*, prepared as directed in the *Assay for iodochlorhydroxyquin*, determined in a 3-mm. cell, exhibits maxima in the region of 7 μ to 11 μ only at the same wavelengths as that of the *Standard preparation* prepared as directed in the *Assay*, similarly measured.

B: A 50-ml. portion of the *Assay preparation*, prepared as directed in the *Assay for hydrocortisone*, meets the requirements of *Identification test B* under *Iodochlorhydroxyquin and Hydrocortisone Cream*, page 371.

Assay for iodochlorhydroxyquin—Proceed as directed in the *Assay for iodochlorhydroxyquin* under *Iodochlorhydroxyquin and Hydrocortisone Cream*, page 371, using an accurately weighed portion of Iodochlorhydroxyquin and Hydrocortisone Lotion equivalent to about 30 mg. of iodochlorhydroxyquin.

Assay for hydrocortisone—Proceed as directed in the *Assay for hydrocortisone* under *Iodochlorhydroxyquin and Hydrocortisone Cream*, page 371.

Packaging and storage—Preserve Iodochlorhydroxyquin and Hydrocortisone Lotion in well-closed containers.

Lotion available—Iodochlorhydroxyquin and Hydrocortisone Lotion usually available contains 3 percent of iodochlorhydroxyquin and 1 percent of hydrocortisone.

CATEGORY—Local anti-infective; glucocorticoid.

APPLICATION—Topically to the affected area 3 or 4 times daily as a lotion containing 3 percent iodochlorhydroxyquin and 1 percent hydrocortisone.

Iodochlorhydroxyquin and Hydrocortisone Ointment

Iodochlorhydroxyquin and Hydrocortisone Ointment contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of C_9H_5ClINO (iodochlorhydroxyquin) and of $C_{21}H_{30}O_5$ (hydrocortisone).

Identification—

A: The infrared absorption spectrum of the *Assay preparation*, prepared as directed in the *Assay for iodochlorhydroxyquin*, determined in a 3-mm. cell, exhibits maxima in the region of 7 μ to 11 μ only at the same wavelengths as that of the *Standard preparation*, prepared as directed in the *Assay*, similarly measured.

B: A 50-ml. portion of the *Assay preparation*, prepared as directed in the *Assay for hydrocortisone*, meets the requirements of *Identification test B* under *Iodochlorhydroxyquin and Hydrocortisone Cream*, page 371.

Weight variation—Iodochlorhydroxyquin and Hydrocortisone Ointment meets the requirements of the weight variation test for ointment.

Assay for iodochlorhydroxyquin—Proceed as directed in the *Assay for iodochlorhydroxyquin* under *Iodochlorhydroxyquin and Hydrocortisone Cream*, page 371, using an accurately weighed portion of Iodochlorhydroxyquin and Hydrocortisone Ointment equivalent to about 30 mg. of iodochlorhydroxyquin.

Assay for hydrocortisone—Proceed as directed in the *Assay for hydrocortisone* under *Iodochlorhydroxyquin and Hydrocortisone Cream*, page 371.

Packaging and storage—Preserve Iodochlorhydroxyquin and Hydrocortisone Ointment in well-closed containers.

Ointments available—Iodochlorhydroxyquin and Hydrocortisone Ointment usually available contains 3 percent of iodochlorhydroxyquin and 0.5 or 1 percent of hydrocortisone.

CATEGORY—Local anti-infective; glucocorticoid.

APPLICATION—Topically to the affected area three or four times daily as an ointment containing 3 percent iodochlorhydroxyquin and 0.5 or 1 percent hydrocortisone.

Compound Iodochlorhydroxyquin Powder

Compound Iodochlorhydroxyquin Powder contains not less than 22.5 percent and not more than 27.5 percent of C_9H_5ClINO.

Iodochlorhydroxyquin	**250 g.**
Lactic Acid	**25 g.**
Zinc Stearate	**200 g.**
Lactose	**525 g.**
To make	**1000 g.**

Mix the lactic acid with the lactose, then add the iodochlorhydroxyquin and the zinc stearate, and mix the Powder.

Identification—Place a quantity of Compound Iodochlorhydroxyquin Powder, equivalent to about 30 mg. of iodochlorhydroxyquin, in a 50-ml. glass-stoppered conical flask, add 20 ml. of 1 *N* sulfuric acid, and shake 5 minutes. Filter, transfer 5 ml. of the filtrate to a glass-stoppered test tube, add 5 drops of potassium dichromate T.S. and 2 ml. of chloroform, and shake well: a red-violet color develops in the chloroform layer.

Assay—Transfer an accurately weighed quantity of Compound Iodochlorhydroxyquin Powder, equivalent to about 50 mg. of iodochlorhydroxyquin, to a 200-ml. volumetric flask, add 100 ml. of 3 *N* hydrochloric acid, and shake mechanically for 15 minutes. Add 3 *N* hydrochloric acid to volume, and mix. Filter a portion of the solution, dilute 4.0 ml. of the filtrate with 3 *N* hydrochloric acid to 200.0 ml., and mix. Concomitantly determine the absorbance of this solution and of a solution of USP Iodochlorhydroxyquin Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 267 mμ, with a suitable spectrophotometer, using 3 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of C_9H_5ClINO in the portion of the Powder taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Compound Iodochlorhydroxyquin Powder in well-closed, light-resistant containers.

CATEGORY—Antitrichomonal (vaginal tract).

APPLICATION—Topically as required.

Iodochlorhydroxyquin Tablets

Iodochlorhydroxyquin Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of C_9H_5ClINO.

Identification—Transfer a portion of finely powdered Iodochlorhydroxyquin Tablets, equivalent to about 25 mg. of iodochlorhydroxyquin, to a 100-ml. volumetric flask, add about 75 ml. of 3 *N* hydrochloric acid, and shake to dissolve the iodochlorhydroxyquin. Add 3 *N* hydrochloric acid to volume, and mix. Filter a portion, and dilute 3 ml. of the filtrate with 3 *N* hydrochloric acid to 100 ml.: the ultraviolet absorption spectrum of the resulting solution exhibits maxima and minima at the same wavelengths as that of USP Iodochlorhydroxyquin Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Iodochlorhydroxyquin Tablets is 30 minutes.

Weight variation, page 901—Iodochlorhydroxyquin Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Iodochlorhydroxyquin Tablets. Transfer a portion of the powder, equivalent to about 100 mg. of iodochlorhydroxyquin and accurately weighed, to a 250-ml. conical flask. Add 50 ml. of ethyl acetate, heat to boiling, and decant the hot, supernatant solution through a filter. Repeat the extraction with three additional 50-ml. portions of ethyl acetate, washing the residue and the filter. Combine the extracts, and evaporate on a steam bath to dryness. Dissolve the residue in about 40 ml. of acetone, add 2 ml. of glacial acetic acid and 20 ml. of a saturated solution of cupric acetate in methanol. Allow the mixture to stand for 5 minutes, and collect the precipitate on a tared, sintered-glass filter. Wash the precipitate with five 5-ml. portions of acetone and five 5-ml. portions of solvent hexane. Dry at 105° to constant weight: the weight of the copper complex so obtained, multiplied by 0.975, represents the weight of C_9H_5ClINO in the portion of the Tablets taken.

Packaging and storage—Preserve Iodochlorhydroxyquin Tablets in tight, light-resistant containers.

Tablets available—Iodochlorhydroxyquin Tablets usually available contain the following amount of iodochlorhydroxyquin: 250 mg.

CATEGORY—Antiamebic.

USUAL DOSE—**250 mg.** three times a day for 10 days; may repeat this 10-day regimen after 8 to 10 days.

USUAL DOSE RANGE—**250** to **500 mg.**

Iodoform

Triiodomethane

CHI_3 Mol. wt. 393.73

Iodoform, previously dried over phosphorus pentoxide for 4 hours, contains not less than 99.0 percent and not more than 100.5 percent of CHI_3.

Description—Iodoform occurs as a fine greenish yellow powder, or lustrous crystals. It has a peculiar, very penetrating, persistent odor. Iodoform is slightly volatile even at ordinary temperatures, and distils slowly with steam.

Solubility—Iodoform is sparingly soluble in alcohol, in glycerin, and in olive oil. It is freely soluble in chloroform and in ether, and is soluble in boiling alcohol. Iodoform is practically insoluble in water to which, however, it imparts its odor and taste.

Melting point, page 814—Iodoform melts to a brown liquid at about 115° and decomposes at a higher temperature, emitting vapors of iodine.

Loss on drying, page 814—Dry Iodoform over phosphorus pentoxide for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Iodoform yields not more than 0.2 percent of residue on ignition.

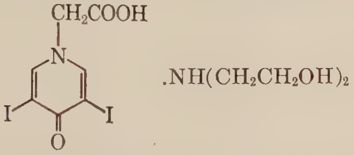
Coloring matter, acids, and alkalies—Shake about 2 g. of Iodoform with 5 ml. of water for 1 minute, and filter: the filtrate is colorless, free from bitter taste, and is neutral to litmus.

Assay—Dissolve about 200 mg. of Iodoform, previously dried over phosphorus pentoxide for 4 hours and accurately weighed, in 20 ml. of alcohol in a 500-ml. glass-stoppered conical flask. Add 30.0 ml. of 0.1 *N* silver nitrate and 10 ml. of nitric acid, stopper the flask, and set it aside overnight. Add 150 ml. of water and 5 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 13.12 mg. of CHI_3.

Packaging and storage—Preserve Iodoform in tight, light-resistant containers, and avoid excessive heat.

CATEGORY—Local anti-infective.

Iodopyracet Injection



3,5-Diiodo-4-oxo-1(4*H*)-pyridineacetic Acid 2,2′-Iminodiethanol (1:1) Compound

$C_{11}H_{16}I_2N_2O_5$ Mol. wt. 510.07

Iodopyracet Injection is a sterile solution of iodopyracet in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{11}H_{16}I_2N_2O_5$.

Description—Iodopyracet Injection occurs as a clear, nearly colorless liquid. It is neutral to litmus. Its specific gravity is about 1.19.

Identification—

A: Dilute 5 ml. of Iodopyracet Injection with 10 ml. of water, and add a slight excess of diluted hydrochloric acid. Collect the liberated acid on a filter and wash thoroughly with cold water. Retain the filtrate and washings. The precipitate of 3,5-diiodo-4-oxo-1(4*H*)-pyridineacetic acid, when dried at 105° for 1 hour, melts between 245° and 249°, page 814.

B: Dilute the combined filtrate and washings from *Identification test A* to 50 ml., cool in ice water, and filter. Evaporate 40 ml. of the filtrate to a syrupy consistency. Add 5 ml. of dehydrated alcohol, neutralize with 1 *N* sodium hydroxide, filter, and dilute to 10 ml. with dehydrated alcohol. Add 1 g. of picric acid, heat to boiling, and cool in ice water. Collect the crystals on a filter, recrystallize from alcohol, and dry over sulfuric acid in vacuum: the picrate so obtained melts between 108° and 110°, page 814. Retain the filtrate. (*Caution: Picrates may be explosive.*)

Residue on ignition, page 858—A 5-ml. portion of Iodopyracet Injection, after evaporation to dryness on a steam bath, yields not more than 5 mg. of residue on ignition (0.1 percent).

Iodide—To 10 ml. of the filtrate from *Identification test B* add 1 ml. of chloroform and 2 drops of ferric chloride T.S., and shake: the chloroform remains free from even a transient red-purple or purplish color.

Pyrogen—Iodopyracet Injection meets the requirements of the *Pyrogen Test*, page 851, the Injection being diluted with an equal volume of sterile water for injection.

Other requirements—Iodopyracet Injection meets the requirements under *Injections*, page 810.

Assay—Pipet into a glass-stoppered, 250-ml. conical flask a volume of Iodopyracet Injection, equivalent to about 350 mg. of iodopyracet. Add 30 ml. of sodium hydroxide solution (1 in 20) and 500 mg. of 30-mesh zinc, and reflux the mixture for 1 hour. Cool to room temperature, wash the condenser with 20 ml. of water, and filter the mixture. Wash the flask and the filter with small portions of water, adding the washings to the filtrate. Add to the filtrate 5 ml. of glacial acetic acid and 1 ml. of tetrabromophenolphthalein ethyl ester T.S., and titrate with 0.05 *N* silver nitrate until the color of the yellow precipitate just changes to green. Each ml. of 0.05 *N* silver nitrate is equivalent to 12.75 mg. of $C_{11}H_{16}I_2N_2O_5$.

Packaging and storage—Preserve Iodopyracet Injection in single-dose containers, preferably of Type I glass.

Injections available—Iodopyracet Injection usually available contains the following amounts of iodopyracet: 3.5 g. in 10 ml.; 7 g. in 20 ml.; 10.5 g. in 30 ml.

CATEGORY—Diagnostic aid (radiopaque–urographic).

USUAL DOSE—Intramuscular and intravenous, **20 ml.**

Ipodate, Calcium, page 121

Ipodate, Calcium, for Oral Suspension, page 122

Ipodate, Sodium, page 649

Ipodate, Sodium, Capsules, page 649

Iso-Alcoholic Elixir

Low-Alcoholic Elixir
High-Alcoholic Elixir, of each a calculated volume

Mix the ingredients.

Low-Alcoholic Elixir

Compound Orange Spirit	**10 ml.**
Alcohol	**100 ml.**
Glycerin	**200 ml.**
Sucrose	**320 g.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Mix the alcohol, glycerin, and 500 ml. of purified water, add the compound orange spirit, agitate thoroughly from time to time, and let stand 24 hours. Filter this solvent mixture through a hard filter paper, returning, if necessary, the first portions of the filtrate until it passes through clear. Dissolve the sucrose in the filtrate by agitation or percolation, and add enough of the solvent mixture to make the product measure 1000 ml.

Alcohol content, page 772—Low-Alcoholic Elixir contains from 8 to 10 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Low-Alcoholic Elixir in tight containers.

High-Alcoholic Elixir

Compound Orange Spirit	**4 ml.**
Saccharin	**3 g.**
Glycerin	**200 ml.**
Alcohol, a sufficient quantity,	
To make	**1000 ml.**

Dissolve the compound orange spirit and the saccharin in 700 ml. of alcohol, add the glycerin and sufficient alcohol to make the product measure 1000 ml., mix well, and filter.

Alcohol content, page 772—High-Alcoholic Elixir contains from 73 to 78 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve High-Alcoholic Elixir in tight containers.

CATEGORY—Vehicle.

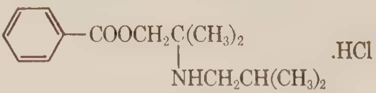
NOTE: Iso-Alcoholic Elixir is intended to serve as a general vehicle for various medicaments that require solvents of different alcohol strengths. When Iso-Alcoholic Elixir is specified in a prescription, the proportion of its two ingredients to be used is that which will produce a solution of the required alcohol strength.

The alcohol strength of the Iso-Alcoholic Elixir to be used with a single liquid galenical in a prescription is approximately the same as that of the galenical.

When galenicals of different alcohol strengths are used in the same prescription, the Iso-Alcoholic Elixir to be used is to be of such alcohol strength as to secure the best solution possible. This will generally be found to be the average of the alcohol strengths of the several ingredients.

For nonextractive substances, the lowest alcohol strength of Iso-Alcoholic Elixir that will yield a perfect solution should be chosen.

Isobucaine Hydrochloride*



2-(Isobutylamino)-2-methyl-1-propanol Benzoate (Ester) Hydrochloride

$C_{15}H_{23}NO_2 . HCl$ Mol. wt. 285.82

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* Patented. See notice, page ii.

Isobucaine Hydrochloride, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{15}H_{23}NO_2 . HCl$.

Description—Isobucaine Hydrochloride occurs as a white, odorless, crystalline solid. The pH of a 1 in 50 solution is about 6.

Solubility—Isobucaine Hydrochloride is freely soluble in water, in alcohol, and in chloroform. It is sparingly soluble in isopropanol, and is very slightly soluble in ether.

Identification—

A: A solution of Isobucaine Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 808.

B: Dissolve about 100 mg. of Isobucaine Hydrochloride in 10 ml. of water, heat almost to boiling, and add, with stirring, 1 ml. of a saturated solution of picric acid in 20 percent alcohol. Cool slowly, collect the precipitate on a filter, wash with a few small portions of water, and dry in a vacuum desiccator over phosphorus pentoxide for 18 hours: the picrate so obtained melts with decomposition at about 180°, page 814. (*Caution: Picrates may be explosive.*)

C: Dissolve about 100 mg. of Isobucaine Hydrochloride in 10 ml. of diluted hydrochloric acid, cool to 0° in an ice bath, and add 5 ml. of sodium nitrite solution (1 in 5) with gentle stirring. Add 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S. and observe immediately: the solution turns green in color, and no bright orange-red precipitate is formed (*absence of a primary aminophenyl group*).

Melting range, page 814—Isobucaine Hydrochloride melts between 182° and 185°.

Loss on drying, page 814—Dry Isobucaine Hydrochloride at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Isobucaine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 600 mg. of Isobucaine Hydrochloride, previously dried at 105° for 4 hours and accurately weighed, to a 200-ml. tall form beaker, dissolve it in 50 ml. of glacial acetic acid, heating if necessary. Add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to the green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 28.58 mg. of $C_{15}H_{23}NO_2 . HCl$.

Packaging and storage—Preserve Isobucaine Hydrochloride in well-closed containers.

CATEGORY—Local anesthetic (dental).

Isobucaine Hydrochloride and Epinephrine Injection

Isobucaine Hydrochloride and Epinephrine Injection is a sterile solution of isobucaine hydrochloride and epinephrine in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{15}H_{23}NO_2 . HCl$ (isobucaine hydrochloride) and not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (epinephrine).

Identification—Isobucaine Hydrochloride and Epinephrine Injection responds to the *Identification tests* under *Isobucaine Hydrochloride*, page 376.

Other requirements—Isobucaine Hydrochloride and Epinephrine Injection meets the requirements under *Injections*, page 810.

Assay for isobucaine hydrochloride—Transfer to a 60-ml. separator an accurately measured volume of Isobucaine Hydrochloride and Epinephrine Injection, equivalent to about 40 mg. of isobucaine hydrochloride. Add water to make 10 ml. and 1 ml. of sodium hydroxide T.S., and completely extract the isobucaine with three 10-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water, filter the chloroform through chloroform-washed cotton, wash the filter with chloroform, add 2 drops of methyl red T.S. to the combined chloroform filtrate and washings, and titrate with 0.01 *N* perchloric acid in dioxane to a red end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* perchloric acid is equivalent to 2.858 mg. of $C_{15}H_{23}NO_2 . HCl$.

Assay for epinephrine—Prepare a *Ferrocitrate solution*, a *Buffer solution*, and a *Standard preparation* as directed under *Epinephrine Assay*, page 803.

Assay preparation—Proceed as directed for *Assay preparation* under *Epinephrine Assay*, page 803.

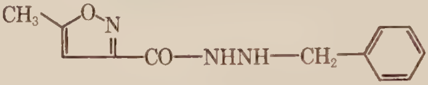
Procedure—Proceed as directed for *Procedure* under *Epinephrine Assay*, page 803. When the *Buffer solution* is added to the *Assay preparation*, an oily precipitate may form. This precipitate should be removed by shaking with 1 ml. of chloroform followed by centrifugation before the spectrophotometric measurements are made using the clear supernatant solution.

Packaging and storage—Preserve Isobucaine Hydrochloride and Epinephrine Injection in single-dose containers, preferably of Type I glass.

Injection available—Isobucaine Hydrochloride and Epinephrine Injection usually available contains the following amounts of isobucaine hydrochloride and epinephrine: 2 percent isobucaine hydrochloride and 1 in 65,000 epinephrine in 1.8-ml. cartridges.

CATEGORY—See Isobucaine Hydrochloride.

Isocarboxazid*



5-Methyl-3-isoxazolecarboxylic Acid 2-Benzylhydrazide

$C_{12}H_{13}N_3O_2$ Mol. wt. 231.26

Isocarboxazid contains not less than 98.5 percent and not more than 100.5 percent of $C_{12}H_{13}N_3O_2$, calculated on the dried basis.

Description—Isocarboxazid occurs as a white or nearly white, crystalline powder. It has a slight, characteristic odor.

Solubility—Isocarboxazid is slightly soluble in water. It is soluble in alcohol and is very soluble in chloroform.

Identification—

A: Dissolve about 10 mg. of Isocarboxazid in 10 ml. of acetone, add 0.2 ml. of water, 0.2 ml. of ammonium molybdate solution (prepared by dissolving 100 mg. of ammonium molybdate in 10 ml. of diluted hydrochloric acid) and mix well: an orange color develops.

B: Dissolve about 15 mg. of Isocarboxazid in alcohol, and add 1 ml. of a *p*-dimethylaminobenzaldehyde solution (prepared by dissolving 100 mg. of *p*-dimethylaminobenzaldehyde in 1 ml. of hydrochloric acid and diluting with alcohol to 100 ml.): a yellow color appears.

Melting range, page 814—Isocarboxazid melts between 105° and 108°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Isocarboxazid, previously dried in vacuum over phosphorus pentoxide at 60° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Isocarboxazid Reference Standard, similarly measured.

Loss on drying, page 814—Dry Isocarboxazid in vacuum over phosphorus pentoxide at 60° for 4 hours: it loses not more than 0.25 percent of its weight.

Residue on ignition, page 858—Isocarboxazid yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—Boil for 2 minutes 100 mg. of Isocarboxazid with 3 ml. of 30 percent hydrogen peroxide, 5 ml. of 2 *N* sodium hydroxide, and 7 ml. of water, cool, and neutralize the solution to litmus with nitric acid: the solution shows no more chloride than corresponds to 0.3 ml. of 0.02 *N* hydrochloric acid (200 parts per million).

Limit of methyl 5-methyl-3-isoxazolecarboxylate and 1-benzyl-3-methyl-5-aminopyrazole—

Standard methyl 5-methyl-3-isoxazole carboxylate preparation—Dissolve 12.5 mg. of NF Methyl 5-methyl-3-isoxazolecarboxylate Reference Standard in sufficient methanol to make 50.0 ml., and mix.

Standard 1-benzyl-3-methyl-5-aminopyrazole preparation—Dissolve 12.5 mg. of NF 1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride Reference Standard in 50.0 ml. of methanol, add 1 g. of sodium carbonate, shake for 2 minutes, and filter. Use the filtrate as directed in the *Procedure.*

Standard isocarboxazid preparation—Prepare a solution of NF Isocarboxazid Reference Standard accurately weighed in methanol containing approximately 50 mg. per ml.

Test preparation—Dissolve 500.0 mg. of Isocarboxazid in sufficient methanol to make 10.0 ml., and mix.

Procedure—Apply 20 µl. each of the *Standard isocarboxazid preparation*, of the *Standard methyl 5-methyl-3-isoxazolecarboxylate preparation*, of the *Standard 1-benzyl-3-methyl-5-aminopyrazole preparation*, and of the *Test preparation* at separate locations on a suitable thin-layer chromatographic plate (see page 791) coated with a 0.25-mm. layer of chromatographic silica gel mixture. Develop the chromatogram in a solvent system consisting of ethyl acetate and *n*-heptane (60:40) until the solvent front has moved about 12 cm. from the origin. Remove the plate from the developing chamber, and examine the chromatogram under shortwave ultraviolet light: any spot produced by the *Test preparation* at about R_f 0.85 does not exceed in magnitude or intensity the spot produced by the *Standard methyl 5-methyl-3-isoxazolecarboxylate preparation* at the same R_f value (0.5 percent). Spray the plate with a freshly prepared mixture consisting of equal volumes of ferric chloride solution (1 in 10) and potassium ferricyanide solution (1 in 5): any spot produced by the *Test preparation* at about R_f 0.25 does not exceed in magnitude or intensity the spot produced by the *Standard 1-benzyl-3-methyl-5-aminopyrazole preparation* at the same R_f value (0.5 percent). The *Standard isocarboxazid preparation* produces a spot at about R_f 0.6.

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* Patented. See notice, page ii.

Assay—Dissolve about 700 mg. of Isocarboxazid, accurately weighed, in 20 ml. of glacial acetic acid, add 20 ml. of hydrochloric acid and 40 ml. of water, and cool to room temperature. Titrate with 0.1 *M* sodium nitrite, determining the end-point electrometrically by means of suitable electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 23.13 mg. of $C_{12}H_{13}N_3O_2$.

Packaging and storage—Preserve Isocarboxazid in well-closed containers.

CATEGORY—Antidepressant.

USUAL DOSE—Initial, **30 mg.** daily as a single dose or in divided doses; maintenance, **10** to **20 mg.** daily.

Isocarboxazid Tablets

Isocarboxazid Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{12}H_{13}N_3O_2$.

Identification—Triturate a quantity of Isocarboxazid Tablets, equivalent to about 15 mg. of isocarboxazid, with 10 ml. of alcohol: the triturate responds to *Identification test B* under *Isocarboxazid*, page 378.

Disintegration, page 878—The disintegration time limit for Isocarboxazid Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Isocarboxazid Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Ammonium molybdate reagent—Dissolve 1 g. of ammonium molybdate in 100 ml. of dilute hydrochloric acid (1 in 10).

Standard preparation—Weigh accurately about 50 mg. of NF Isocarboxazid Reference Standard, dissolve in sufficient acetone to make 250.0 ml., and mix.

Assay preparation—Weigh and finely powder not less than 20 Isocarboxazid Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg. of isocarboxazid, to a 50-ml. volumetric flask, add acetone to volume, and mix. Shake well, centrifuge to clarify, and use the clear supernatant liquid as directed in the *Procedure*.

Procedure—Transfer to separate 100-ml. volumetric flasks 5.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of acetone to serve as the blank. To each flask add 1.0 ml. of water, 50.0 ml. of acetone, and 1.0 ml. of *Ammonium molybdate reagent*. Stopper the flasks, mix, and allow to stand for 30 minutes with occasional swirling. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 420 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{12}H_{13}N_3O_2$ in the portion of the Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Isocarboxazid Tablets in well-closed, light-resistant containers.

Tablets available—Isocarboxazid Tablets usually available contain the following amount of isocarboxazid: 10 mg.

CATEGORY and DOSE—See Isocarboxazid.

Isoflurophate Ophthalmic Ointment

$[(CH_3)_2CHO]_2FPO$

Diisopropyl Phosphorofluoridate

$C_6H_{14}FO_3P$ Mol. wt. 184.15

Isoflurophate Ophthalmic Ointment contains not less than 0.0225 percent and not more than 0.0275 percent of $C_6H_{14}FO_3P$ in a suitable, anhydrous base.

Identification—Place about 100 mg. of Isoflurophate Ophthalmic Ointment in the right eye of each of 3 rabbits, and examine the eye 18 to 20 hours later: the average diameter of the pupils of the treated eyes is at least 2 mm. smaller than the average diameter of the pupils of the untreated eyes.

Irritation—The conjuctivas of the eyes treated as directed in the *Identification test*, as compared with those of the untreated eyes, after 1 hour, show not more than a slight reddening, which practically disappears in 4 hours.

Weight variation, page 901—Isoflurophate Ophthalmic Ointment meets the requirements of the weight variation test for ointments.

Metal particles—Isoflurophate Ophthalmic Ointment meets the requirements of the test for *Metal Particles—Ophthalmic Ointments*, page 816.

Water, page 900—Dissolve about 10 g. of Isoflurophate Ophthalmic Ointment, accurately weighed, in a mixture of 25 ml. each of absolute methanol and of toluene, and determine the water content by the titrimetric method: not more than 0.03 percent is found.

Assay—

Standard preparation—Pipet into a 250-ml. volumetric flask 3.0 ml. of phosphate solution (154.0 mg. of dried KH_2PO_4 in water to make 500.0 ml.), add 7.5 g. of zinc oxide, 30 ml. of water, and 25 ml. of 10 *N* sulfuric acid, and heat on a steam bath, if necessary, until the zinc oxide has dissolved. Cool, dilute to volume with water, and mix.

Assay preparation—Weigh accurately about 2 g. of Isoflurophate Ophthalmic Ointment in a small porcelain crucible, and cover it with 3.0 g. of zinc oxide. Apply heat intermittently with a low flame to allow the oil to burn off. Then ignite continuously at 700° to 800°, preferably in a muffle furnace, to remove all or nearly all of the carbon. Allow the crucible to cool, and place it in a 250-ml. beaker, loosening the contents by tapping the crucible against the side of the beaker. Add 30 ml. of water and 10 ml. of 10 *N* sulfuric acid, and heat on a hot plate or steam bath, with occasional stirring, until solution is complete. Remove the crucible from the solution, and rinse it with a few ml. of water, collecting the rinsings in a beaker. Cool the solution, quantitatively transfer it to a 100-ml. volumetric flask, add water to volume, and mix.

Procedure—Pipet 50.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate 100-ml. volumetric flasks, then treat each as follows: Add, dropwise, sodium carbonate solution (1 in 5), swirling the flask after each addition, until a permanent turbidity is produced. Add 10 ml. of 10 *N* sulfuric acid and 10 ml. of molybdate reagent (5 g. of ammonium molybdate in 1 *N* sulfuric acid to make 100 ml.). Add, with mixing, 5 ml. of freshly prepared stannous chloride solution (dissolve 1.0 g. of stannous chloride in 5 ml. of hydrochloric acid and dilute with water to 500 ml.), add water to volume, mix, and 10 minutes after the addition of the stannous chloride, measure the absorbance of each solution at 710 mμ with a suitable spectrophotometer. Calculate the quantity, in mg., of $C_6H_{14}FO_3P$ in the weight of Isoflurophate Ophthalmic Ointment taken by the formula $2W \times 1.938 \times (A_U/A_S)$, in which W is the weight, in mg., of PO_4 in the volume of *Standard preparation* taken, 1.938 is the conversion factor from PO_4 to $C_6H_{14}FO_3P$, A_U is the absorbance of the solution from the *Assay preparation*, and A_S is that from the *Standard preparation*.

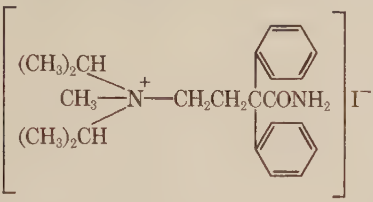
Packaging and storage—Preserve Isoflurophate Ophthalmic Ointment in collapsible ophthalmic ointment tubes.

Labeling—The label of Isoflurophate Ophthalmic Ointment bears the expiration date, which is not more than 2 years after date of manufacture.

CATEGORY—Cholinergic (ophthalmic).

APPLICATION—Topically to conjunctiva once every 3 days to three times a day.

Isopropamide Iodide*



(3-Carbamoyl-3,3-diphenylpropyl)diisopropylmethylammonium Iodide

$C_{23}H_{33}IN_2O$ Mol. wt. 480.44

Isopropamide Iodide, dried in vacuum at 60° for 2 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_{23}H_{33}IN_2O$.

Description—Isopropamide Iodide occurs as a white to pale yellow crystalline powder and has a bitter taste.

Solubility—Isopropamide Iodide is sparingly soluble in water and is freely soluble in chloroform and in alcohol. It is very slightly soluble in benzene and in ether.

Identification—

A: To 5 ml. of a solution of Isopropamide Iodide (1 in 1000), add 5 ml. of sodium carbonate solution (1 in 100), 0.5 ml. of bromophenol blue T.S., and 10 ml. of chloroform, and shake for several minutes: the chloroform layer becomes an intense blue.

B: A solution of Isopropamide Iodide (1 in 1000) responds to the tests for *Iodide,* page 808.

Infrared absorption, page 866—The infrared absorption spectrum of a 2 in 25 solution in chloroform of Isopropamide Iodide, previously dried in vacuum at 60° for 2 hours, determined in a 0.1-mm. cell, exhibits maxima only at the same wavelengths as that of NF Isopropamide Iodide Reference Standard, similarly measured.

Loss on drying, page 814—Dry Isopropamide Iodide in vacuum at 60° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Transfer about 1 g. of Isopropamide Iodide, accurately weighed, to a tared porcelain crucible. Ignite carefully, using a low flame, until the sample is practically free of carbon, and then heat the residue in a muffle furnace at 550° for 4 hours. Cool the crucible in a desiccator, and weigh. Isopropamide Iodide yields not more than 0.5 percent of residue on ignition.

Assay—Dissolve about 750 mg. of Isopropamide Iodide, dried in vacuum at 60° for 2 hours and accurately weighed, in 60 ml. of glacial acetic acid, add 15 ml. of mercuric acetate T.S. and 3 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 48.04 mg. of $C_{23}H_{33}IN_2O$.

Packaging and storage—Preserve Isopropamide Iodide in well-closed, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**5 mg.** two times a day.

USUAL DOSE RANGE—**10** to **20 mg.** daily.

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* Patented. See notice, page ii.

Isopropamide Iodide Tablets

Isopropamide Iodide Tablets contain an amount of $C_{23}H_{33}IN_2O$ (isopropamide iodide) equivalent to not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{23}H_{33}N_2O$ (isopropamide).

Identification—Triturate a portion of powdered Isopropamide Iodide Tablets, equivalent to about 10 mg. of isopropamide, with 10 ml. of water, and filter. The filtrate responds to the *Identification tests* under *Isopropamide Iodide,* page 381.

Disintegration, page 878—The disintegration time limit for Isopropamide Iodide Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Isopropamide Iodide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Crush and quantitatively transfer one tablet to a 100-ml. volumetric flask with about 50 ml. of water, and shake mechanically for 30 minutes. Dilute to volume with water, mix well, and filter, discarding the first 20 ml. of filtrate. Concomitantly determine the absorbance of this solution and of a solution of NF Isopropamide Iodide Reference Standard, in the same medium at a concentration of about 70 mcg. per ml., in 5-cm. cells, at 280 mμ and at the maximum at about 258 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{23}H_{33}N_2O$ (isopropamide) in the tablet by the formula, $(T/D) \times 0.7359C \times (A_{U258} - A_{U280})/(A_{S258} - A_{S280})$, in which T is the labeled quantity, in mg., of isopropamide in the tablet; D is the exact concentration, in mcg. per ml., of isopropamide in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; 0.7358 is the factor converting isopropamide iodide to isopropamide; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_{U258} and A_{U280} are the absorbances of the sample solution at 258 mμ and 280 mμ, respectively; and A_{S258} and A_{S280} are the absorbances of the Reference Standard solution at 258 mμ and 280 mμ, respectively.

Assay—

Ion-exchange column—Insert a small pledget of glass wool in the bottom of a 240 × 6-mm. glass tube fitted with a stopcock, fill the tube with water, and add an aqueous slurry of a suitable anion-exchange resin, chloride form (previously soaked in water for at least 24 hours prior to use), until a height of about 200 mm. is reached. Wash the column with 50 ml. of water, and use without delay.

Standard preparation—Transfer about 135 mg. of NF Isopropamide Iodide Reference Standard, accurately weighed, to a 250-ml. volumetric flask, and dissolve in 150 ml. of water. Add 5 ml. of aluminum chloride solution (1 in 10) and 2 ml. of stronger ammonia T.S., then dilute to volume with water, mix, and filter, discarding the first 15 ml. of filtrate. Use the subsequent filtrate as directed in the *Procedure*.

Assay preparation—Weigh and finely powder not less than 25 Isopropamide Iodide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg. of isopropamide, to a 250-ml. volumetric flask, add 150 ml. of water, and shake mechanically for 60 minutes. Add 5 ml. of aluminum chloride solution (1 in 10) and 2 ml. of stronger ammonia T.S., then dilute to volume with water, mix, and filter, discarding the first 15 ml. of filtrate. Use the subsequent filtrate as directed in the *Procedure*.

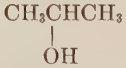
Procedure—Pipet 50.0 ml. each of the *Standard preparation* and of the *Assay preparation* onto separate ion-exchange columns, and collect the eluates in separate 200-ml. volumetric flasks. Regulate the flow of effluent so that it does not exceed 40 drops per minute, and when the liquid level reaches the top of each column, add successively two 5-ml. portions and one 10-ml. portion of water to each column, allowing each portion to just enter the column before adding the next portion of water. After the eluates have been collected, dilute each flask to volume with water, and mix. Concomitantly determine the absorbances of the solutions in 5-cm. cells, at 280 mμ and at the maximum at about 258 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbances of the solution from the *Standard preparation* at 258 mμ and at 280 mμ as A_{S258} and A_{S280}, respectively, and the absorbances of the solution from the *Assay preparation* at 258 mμ and at 280 mμ as A_{U258} and A_{U280}, respectively. Calculate the quantity, in mg., of $C_{23}H_{33}N_2O$ (isopropamide) in the portion of Tablets taken by the formula $0.25C \times 0.7359 \times (A_{U258} - A_{U280})/(A_{S258} - A_{S280})$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and 0.7359 is the factor converting isopropamide iodide to isopropamide.

Packaging and storage—Preserve Isopropamide Iodide Tablets in well-closed containers.

Tablets available—Isopropamide Iodide Tablets usually available contain isopropamide iodide equivalent to the following amount of isopropamide: 5 mg.

CATEGORY and DOSE—See Isopropamide Iodide.

Isopropyl Alcohol



$$CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$$

2-Propanol

C_3H_8O Mol. wt. 60.10

Isopropyl Alcohol contains not less than 99.0 percent and not more than 100.5 percent, by weight, of C_3H_8O.

Description—Isopropyl Alcohol is a transparent, colorless, mobile, and volatile liquid. It has a characteristic odor and a slightly bitter taste.

Solubility—Isopropyl Alcohol is miscible with water, with alcohol, with ether, and with chloroform.

Identification—To 2 ml. of Isopropyl Alcohol contained in a test tube, add 3 ml. of water and 1 ml. of mercuric sulfate T.S., and warm gently: a white or yellowish precipitate or turbidity is formed.

Specific gravity, page 866—The specific gravity of Isopropyl Alcohol is not less than 0.783 and not more than 0.787, indicating not less than 99.0 percent and not more than 100.5 percent, by weight, of C_3H_8O.

Distilling range, *Method I,* page 782—Isopropyl Alcohol distils completely between 81° and 83°.

Refractive index, page 858—The refractive index of Isopropyl Alcohol is not less than 1.376 and not more than 1.378 at 20°.

Acidity—To 50 ml. of Isopropyl Alcohol in a suitable flask add 100 ml. of carbon dioxide-free water. Add 2 drops of phenolphthalein T.S., and titrate with 0.02 *N* sodium hydroxide to a pink color that persists for 30 seconds. Not more than 0.7 ml. of 0.02 *N* sodium hydroxide is required for neutralization.

Nonvolatile residue—Evaporate 50 ml. of Isopropyl Alcohol to dryness in a tared porcelain dish on a steam bath and heat at 105° for 1 hour: the weight of the residue does not exceed 2.5 mg. (50 parts per million, w/v).

Packaging and storage—Preserve Isopropyl Alcohol in tight containers.

Category—Solvent.

Isopropyl Rubbing Alcohol

Isopropyl Rubbing Alcohol contains not less than 68.0 percent and not more than 72.0 percent of isopropyl alcohol, by volume, the remainder consisting of water, with or without color additives certified by the federal Food and Drug Administration for use in drugs, suitable stabilizers, and perfume oils.

Description—Isopropyl Rubbing Alcohol is a transparent, mobile, and volatile liquid having a slightly bitter taste and, in the absence of added odorous constituents, a characteristic odor.

Identification—To 2 ml. of Isopropyl Rubbing Alcohol contained in a test tube, add 2 ml. of water and 1 ml. of mercuric sulfate T.S., and warm gently: a white or yellowish precipitate or turbidity is formed.

Specific gravity, page 866—The specific gravity of Isopropyl Rubbing Alcohol is not less than 0.869 and not more than 0.879.

Acidity—Transfer 50 ml. of Isopropyl Rubbing Alcohol into a suitable flask and add about 75 ml. of carbon dioxide-free water. Titrate immediately with 0.02 *N* sodium hydroxide, using 3 drops of phenolphthalein T.S. as the indicator, to a pink color that persists for 30 seconds: not more than 1 ml. of 0.02 *N* sodium hydroxide is required for neutralization.

Nonvolatile residue—Evaporate 50 ml. of Isopropyl Rubbing Alcohol to dryness in a tared porcelain dish on a steam bath and dry at 105° for 1 hour: the weight of the residue does not exceed 50 mg. (0.1 percent).

Assay—Pipet 50.0 ml. of Isopropyl Rubbing Alcohol into a 250-ml. distilling flask, note its temperature, and add 100 ml. of water. Arrange the flask for distillation, distil, and collect 95 ml. of distillate in a 100-ml. volumetric flask. Adjust to the temperature at which the original test liquid was measured, and add water to volume. Mix, and determine the specific gravity of the distillate at 25° (see page 866). The specific gravity is no greater than 0.955, corresponding to 68.0 percent, and no less than 0.950, corresponding to 72.0 percent of isopropyl alcohol in the original sample.

Packaging and storage—Preserve Isopropyl Rubbing Alcohol in tight containers.

Category—Rubefacient.

Isoproterenol Sulfate Aerosol

Isoproterenol Sulfate Aerosol is a suspension of microfine isoproterenol sulfate in fluorochlorohydrocarbon propellants in a pressurized container. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of

$(C_{11}H_{17}NO_3)_2.H_2SO_4$, and it delivers not less than 75.0 percent and not more than 125.0 percent of the labeled amount of $(C_{11}H_{17}NO_3)_2.H_2SO_4$ per inhalation through an oral inhalation actuator.

Identification—

A: Place 10 ml. of water in a small beaker, and fire 10 sprays from Isoproterenol Sulfate Aerosol under the surface of the water, actuating the valve by pressing the container against the bottom of the beaker. Filter, and to 5 ml. of the filtrate add 1 drop of 0.1 *N* hydrochloric acid. Add 0.5 ml. of 0.1 *N* iodine, allow to stand for 5 minutes, and add 1 ml. of 0.1 *N* sodium thiosulfate: a red-brown color is produced.

B: A portion of the filtrate obtained in *Identification test A* responds to the tests for *Sulfate*, page 810.

Unit spray content—

Unit spray sampling apparatus—Prepare as directed under *Aerosols*, page 770.

Ferro-citrate solution and *Buffer solution*—Prepare as directed under *Epinephrine Assay*, page 803.

Standard preparation—Transfer about 50 mg. of USP Isoproterenol Hydrochloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add a freshly prepared solution of sodium bisulfite (1 in 500) to volume, and mix. Transfer 5.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with the sodium bisulfite solution, and mix.

Test preparation—Transfer 30.0 ml. of a freshly prepared solution of sodium bisulfite (1 in 500) to the collection chamber of the apparatus, and clamp the intake tube in a horizontal position. Fit the aerosol container with its oral inhalation actuator, and prime the unit by alternately shaking and firing it 10 times. Couple the unit to the intake tube of the apparatus, and adjust the air flow to a rate of 10 to 15 liters per minute. Remove the container, leaving the actuator in place. Shake the container, seat it in the actuator, and immediately deliver a single spray into the system. Deliver a total of 10 sprays in this manner. Remove the container and actuator from the assembly, clamp the intake tube in a vertical position, and scavenge the drug remaining in the intake system as follows: disconnect the collection chamber, transfer the sample solution to a small beaker, and then wash the inside of the intake tube with the sample solution, collecting the washings in the collection chamber placed a few cm. below its normal position. Connect the collection chamber into the system again, and draw the sample solution into it through the bubbler and intake tube. Recycle the sample solution two times in this manner, then add 15 ml. of chloroform to the collection chamber, stopper it, and shake vigorously for 5 minutes. Use the clear supernatant solution as directed in the *Procedure*.

Procedure—Proceed as directed for *Procedure* in the *Assay*. Calculate the quantity, in mg., of $(C_{11}H_{17}NO_3)_2.H_2SO_4$ delivered per spray by the formula $0.03 \times 1.051 \times (C/10) \times (A_U/A_S)$, in which 1.051 is the ratio of one-half the molecular weight of isoproterenol sulfate (anhydrous) to the molecular weight of isoproterenol hydrochloride (anhydrous), and C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Particle size—Prime the valve of Isoproterenol Sulfate Aerosol by alternately shaking and firing it several times, and then actuate one measured spray onto a clean, dry microscope slide held 5 cm. from the end of the oral inhalation actuator, perpendicular to the direction of the spray. Carefully rinse the slide with about 2 ml. of carbon tetrachloride, and allow to dry. Examine the slide under a microscope, equipped with a calibrated ocular micrometer, using 450× magnification. Focus on the particles of 25 fields of view near the center of the sample pattern, and note the size of the great majority of individual particles: they are less than 5 μ in diameter; record the number and size of all individual crystalline particles (not agglomerates) more than 10 μ in length measured along the longest axis: not more than 10 such particles are observed.

Other requirements—Isoproterenol Sulfate Aerosol meets the requirements for *Leak Testing* under *Aerosols*, page 770.

Assay—

Ferro-citrate solution and *Buffer solution*—Prepare as directed under *Epinephrine Assay*, page 803.

Container sampling apparatus—Prepare as directed under *Aerosols*, page 770.

Standard preparation—Transfer about 50 mg. of USP Isoproterenol Hydrochloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add a freshly prepared solution of sodium bisulfite (1 in 500) to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with the sodium bisulfite solution, and mix.

Assay preparation—Transfer 10 ml. of chloroform and 20.0 ml. of a freshly prepared solution of sodium bisulfite (1 in 500) to the tube of the apparatus, and connect the tube with the firing adapter. Prime the valve of Isoproterenol Sulfate Aerosol by alternately shaking and firing it 10 times through a clean actuator. Accurately weigh the Aerosol, shake it, seat the valve stem in the firing adapter inlet hole, and then press down firmly to deliver a single spray. Deliver a total of 10 sprays in this manner. Weigh the Aerosol, and determine the total weight of the 10 sprays. Place a finger over the inlet hole of the firing adapter, and shake vigorously for 1 minute. Transfer the mixture to a centrifuge tube, and centrifuge for 5 minutes. Use the clear supernatant solution as directed in the *Procedure.*

Procedure—Transfer 10.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate test tubes. To each tube add 0.1 ml. of *Ferro-citrate solution* and 1.0 ml. of *Buffer solution,* and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 530 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$ in each ml. of the Aerosol by the formula $0.02C \times 1.051 \times (d/W) \times (A_U/A_S)$, in which C is the exact concentration of the *Standard preparation,* in mcg. per ml., 1.051 is the ratio of one-half the molecular weight of isoproterenol sulfate (anhydrous) to the molecular weight of isoproterenol hydrochloride (anhydrous), W is the weight of the sample taken, in g., and d is the density, in g. per ml., of the Aerosol, determined as follows: Weigh a known volume (v) of the Aerosol in a suitable 5-ml. gas-tight syringe equipped with a linear valve. Calibrate the volume of the syringe by filling to the 5-ml. mark with dichlorotetrafluoroethane withdrawn from a plastic-coated glass vial sealed with a neoprene multiple-dose rubber stopper and an aluminum seal, using 1.456 g. per ml. as the density of the calibrating liquid. Maintain the dichlorotetrafluoroethane, the Aerosol sample, and the syringe (protected from becoming wet) at 25° in a water bath. Obtain the sample, equivalent to the same volume as that obtained during the sampling procedure, from the Aerosol by means of a sampling device consisting of a replaceable rubber septum engaged in the plate threads at one end of a threaded fitting, the opposite end of which contains a sharpened tube capable of puncturing the aerosol container, and a rubber gasket around the tube to prevent leakage of the container contents after puncture.* Record the weight of the volume (v) of the Aerosol as w, and calculate the density by the formula w/v.

Packaging and storage—Preserve Isoproterenol Sulfate Aerosol in small, nonreactive, light-resistant aerosol containers equipped with metered-dose valves and provided with oral inhalation actuators.

Aerosol available—Isoproterenol Sulfate Aerosol usually available contains 2 mg. of isoproterenol sulfate per ml. of aerosol, and delivers 80 mcg. of isoproterenol sulfate per inhalation.

Category—Adrenergic (bronchodilator).

Usual dose of isoproterenol sulfate—Oral inhalation, **80** to **160 mcg.** in an aerosol, allowing at least 2 minutes to elapse between inhalations.

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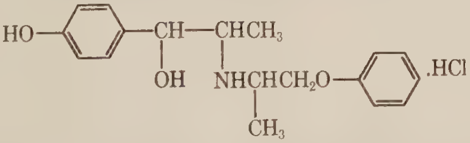
* A suitable sampling system is available from Alltek Associates, PO Box 498, Arlington Heights, IL 60006.

Isoxsuprine Hydrochloride*



p-Hydroxy-α-[1-[(1-methyl-2-phenoxyethyl)amino]ethyl]benzyl Alcohol Hydrochloride

$C_{18}H_{23}NO_3 \cdot HCl$ Mol. wt. 337.85

Isoxsuprine Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{18}H_{23}NO_3 \cdot HCl$, calculated on the dried basis.

Description—Isoxsuprine Hydrochloride occurs as a white, crystalline powder having a bitter taste. It is odorless.

Solubility—Isoxsuprine Hydrochloride is slightly soluble in water and is sparingly soluble in alcohol.

Identification—

A: To 1 ml. of a solution of Isoxsuprine Hydrochloride (1 in 100) add stronger ammonia water until the solution is just alkaline to litmus, and then add 5 ml. of a solution of sodium nitrite (1 in 15) in diluted sulfuric acid: a yellow precipitate forms which dissolves upon the addition of sodium hydroxide solution (1 in 5).

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* Patented. See notice, page ii.

B: To 1 ml. of a solution of Isoxsuprine Hydrochloride (1 in 100) add 1 ml. of phosphomolybdic acid solution (1 in 100): a pale yellow to white precipitate forms.

Melting range, *Class Ia,* page 815—Isoxsuprine Hydrochloride melts between 201° and 208°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Isoxsuprine Hydrochloride, previously dried at 105° for 1 hour, exhibits maxima only at the same wavelengths as that of NF Isoxsuprine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Isoxsuprine Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Isoxsuprine Hydrochloride Reference Standard, similarly measured.

pH, page 824—The pH of a solution of Isoxsuprine Hydrochloride (1 in 100) is between 4.5 and 6.0.

Loss on drying, page 814—Dry Isoxsuprine Hydrochloride at 105° for 1 hour: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Isoxsuprine Hydrochloride yields not more than 0.2 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Isoxsuprine Hydrochloride is 20 parts per million.

Assay—Transfer about 50 mg. of Isoxsuprine Hydrochloride, accurately weighed, to a 1000-ml. volumetric flask, add water to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Isoxsuprine Hydrochloride Reference Standard, in the same medium, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at 269 mμ and at 300 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{18}H_{23}NO_3.HCl$ in the Isoxsuprine Hydrochloride taken by the formula $C \times (A_{U269} - A_{U300})/(A_{S269} - A_{S300})$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_{U269} and A_{U300} are the absorbances of the sample solution at 269 mμ and 300 mμ, respectively, and A_{S269} and A_{S300} are the absorbances of the Reference Standard solution at 269 mμ and 300 mμ, respectively.

Packaging and storage—Preserve Isoxsuprine Hydrochloride in tight containers.

CATEGORY—Vasodilator.

USUAL DOSE RANGE—**10 mg.** to **20 mg.** three or four times a day.

Isoxsuprine Hydrochloride Tablets

Isoxsuprine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{23}NO_3.HCl$.

Identification—Transfer a portion of finely powdered Isoxsuprine Hydrochloride Tablets, equivalent to about 10 mg. of isoxsuprine hydrochloride, to a 60-ml. separator, add 10 ml. of pH 9.0 alkaline borate buffer, and shake vigorously to mix. Extract with 2 ml. of chloroform, filter the extract through a pledget of cotton, and mix the filtrate with 500 mg. of potassium bromide. Evaporate the chloroform, carefully removing the last trace of solvent in a small vacuum flask, and use the residue to prepare a potassium bromide dispersion. The infrared absorption spectrum of the potassium bromide dispersion of the isoxsuprine so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of NF Isoxsuprine Hydrochloride Reference Standard, which has been treated in the same manner as the sample.

Disintegration, page 878—The disintegration time limit for Isoxsuprine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Isoxsuprine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Isoxsuprine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of isoxsuprine hydrochloride, to a 250-ml. separator containing 50 ml. of 0.2 *M* disodium phosphate. Stopper the separator, and shake vigorously to effect complete dispersion. Extract with four 20-ml. portions of chloroform, filtering each extract through cotton into a 250-ml. separator. Extract the combined filtrates with four 20-ml. portions of 0.1 *N* hydrochloric acid. Collect the aqueous extracts in a 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Transfer 10.0 ml. into a 100-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Isoxsuprine Hydrochloride Reference Standard, in the same medium, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at 269 mμ and at 300 mμ, with a suitable spectrophotometer, using 0.01 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{18}H_{23}NO_3.HCl$ in the portion of the Tablets taken by the formula $C \times (A_{U269} - A_{U300})/(A_{S269} - A_{S300})$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_{U269} and A_{U300} are the absorbances of the sample solution at 269 mμ and 300 mμ, respectively, and A_{S269} and A_{S300} are the absorbances of the Reference Standard solution at 269 mμ and 300 mμ, respectively.

Packaging and storage—Preserve Isoxsuprine Hydrochloride Tablets in tight containers.

Tablets available—Isoxsuprine Hydrochloride Tablets usually available contain the following amount of isoxsuprine hydrochloride: 10 mg.

CATEGORY and DOSE—See Isoxsuprine Hydrochloride.

Juniper Tar

Juniper Tar is the empyreumatic volatile oil obtained from the woody portions of *Juniperus oxycedrus* Linné (Fam. *Pinaceæ*).

Description—Juniper Tar is a dark brown, clear, thick liquid, having a tarry odor and a faintly aromatic, bitter taste.

Solubility—Juniper Tar is very slightly soluble in water. One volume of Juniper Tar dissolves in 9 volumes of alcohol. It dissolves in 3 volumes of ether, leaving only a slight, flocculent residue. Juniper Tar is only partially soluble in solvent hexane. It is miscible with amyl alcohol, with chloroform, and with glacial acetic acid.

Identification—Shake 1 volume of Juniper Tar with 20 volumes of warm water, filter, and use the filtrate for the following tests:

A: To 5 ml. of the cold filtrate add a few drops of silver-ammonium nitrate T.S.: a black color is produced.

B: To 5 ml. of the filtrate add a few drops of alkaline cupric tartrate T.S., and heat the solution to boiling: a red precipitate is formed.

Specific gravity, page 866—The specific gravity of Juniper Tar is not less than 0.950 and not more than 1.055.

Reaction—The filtrate prepared for the *Identification tests* is acid to litmus.

Rosin or rosin oils—Triturate 1 ml. of Juniper Tar with 15 ml. of solvent hexane, filter the solution, add an equal volume of cupric acetate solution (1 in 100), shake vigorously, and allow the liquids to separate. Decant the solvent hexane layer into a test tube, and add an equal volume of ether: the liquid does not become intensely green and is not darker than brown.

Packaging and storage—Preserve Juniper Tar in tight, light-resistant containers, and avoid exposure to excessive heat.

CATEGORY—Local anti-eczematic.

FOR EXTERNAL USE—Topically as 1 to 5 percent ointment.

Kaolin

Kaolin is a native hydrated aluminum silicate, powdered and freed from gritty particles by elutriation.

Description—Kaolin occurs as a soft, white or yellowish white powder, or as lumps. It has an earthy or clay-like taste and, when moistened with water, assumes a darker color and develops a marked clay-like odor.

Solubility—Kaolin is insoluble in water, in cold dilute acids, and in solutions of the alkali hydroxides.

Identification—Mix 1 g. of Kaolin with 10 ml. of water and 5 ml. of sulfuric acid in a porcelain dish. Evaporate the mixture until the excess of water is removed, and further heat the residue until dense white fumes of sulfur trioxide appear; then cool, cautiously add 20 ml. of water, boil for a few minutes, and filter: there remains on the filter a gray residue (*impure silica*). The filtrate responds to the tests for *Aluminum*, page 807.

Loss on ignition—Kaolin loses not more than 15 percent of its weight upon ignition between 550° and 600°.

Acid-soluble substances—Digest 1 g. of Kaolin with 20 ml. of diluted hydrochloric acid for 15 minutes, and filter: 10 ml. of the filtrate evaporated to dryness and ignited leaves not more than 10 mg. of residue (2 percent).

Carbonate—Mix 1 g. of Kaolin with 10 ml. of water and 5 ml. of sulfuric acid: no effervescence occurs.

Iron—Triturate 2 g. of Kaolin in a mortar with 10 ml. of water and add 500 mg. of sodium salicylate: the mixture does not acquire more than a slight reddish tint.

Lead—To 1 g. of Kaolin contained in a centrifuge tube add 10 ml. of 5 percent nitric acid and digest for 1 hour in a boiling water bath. Centrifuge until the solids are completely separated and pour the supernatant liquid into a 100-ml. volumetric flask. Add 5 ml. of 5 percent nitric acid to the Kaolin, mix well, and digest for 15 minutes in a boiling water bath. Centrifuge, and add the supernatant liquid to the previous extract in the volumetric flask. Dilute to volume with water. A 50-ml. portion of this solution contains not more than 5 mcg. of lead (corresponding to not more than 10 parts per million) when tested according to the *Lead Limit Test*, page 813, using 3 ml. of ammonium citrate solution, 1 ml. of potassium cyanide solution, and 0.5 ml. of hydroxylamine hydrochloride solution.

Packaging and storage—Preserve Kaolin in well-closed containers.

CATEGORY—Adsorbent.

Kaolin Mixture with Pectin

Kaolin	**200**	**g.**
Pectin	**10**	**g.**
Tragacanth, powdered	**5**	**g.**
Benzoic Acid	**2**	**g.**
Sodium Saccharin	**1**	**g.**
Glycerin	**20**	**ml.**
Peppermint Oil	**0.75**	**ml.**
Purified Water, a sufficient quantity,		
To make	**1000**	**ml.**

Mix the kaolin with 500 ml. of purified water. Triturate the pectin, powdered tragacanth, and sodium saccharin with the glycerin and add to this, with constant stirring, the benzoic acid dissolved in 300 ml. of boiling purified water. Allow the mixture to stand until it cools to room temperature and all the pectin is dissolved. Add the peppermint oil and the kaolin–water mixture, mix thoroughly, and finally add sufficient purified water to make 1000 ml.

In order to obtain a product with suitable consistency when larger amounts are prepared, the quantity of tragacanth and, if necessary, the quantity of pectin may be altered. However, if the proportion of pectin in the formula is altered by more than 10 percent, the pectin content of the preparation must be clearly stated on the label.

Identification—Mix 850 mg. of the residue, obtained in the determination of *Residue on ignition*, with 12 ml. of water and 5 ml. of sulfuric acid in a porcelain crucible. Heat the mixture until the excess of water is removed and dense white fumes of sulfur trioxide appear. Cool, cautiously add 20 ml. of water, boil for a few minutes, and filter: a gray residue of impure silica remains on the filter. The filtrate responds to the tests for *Aluminum*, page 807.

Specific gravity, page 866—The specific gravity of Kaolin Mixture with Pectin is not less than 1.10 and not more than 1.15.

Residue on ignition—Weigh accurately about 10 g. of Kaolin Mixture with Pectin in a tared evaporating dish. Determine the volume by dividing its weight by the specific gravity. Evaporate on a steam bath and ignite at red heat to constant weight. The weight of the residue on ignition of Kaolin Mixture with Pectin is not less than 17.5 g. and not more than 19.5 g. in each 100 ml. (17.5 to 19.5 percent).

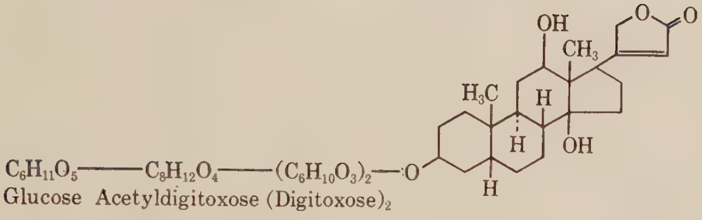
Salmonella, page 862—The test for *Salmonella* in Kaolin Mixture with Pectin is negative.

Packaging and storage—Preserve Kaolin Mixture with Pectin in tight containers.

CATEGORY—Adsorbent (antidiarrheal).
USUAL DOSE—**30 ml.** as needed.

Lactate, Calcium, page 123
Lactate, Calcium, Tablets, page 123
Lactated Potassic Saline Injection, page 569

Lanatoside C


OH
CH3
O
O
H3C
H
H
OH
H
C6H11O5——C8H12O4——(C6H10O3)2—O
Glucose Acetyldigitoxose (Digitoxose)2

$C_{49}H_{76}O_{20}$ Mol. wt. 985.14

Lanatoside C contains not less than 98.0 percent and not more than 102.0 percent of $C_{49}H_{76}O_{20}$, calculated on the dried basis.

Caution: Lanatoside C is extremely poisonous.

Description—Lanatoside C occurs as colorless or white crystals or as a white, crystalline powder. It is odorless. It melts indistinctly, and with decomposition, above 240° after previous sintering. It is hygroscopic, rapidly absorbing about 7 percent of moisture when exposed to air.

Solubility—Lanatoside C is insoluble in water. It is soluble in dioxane, in pyridine, and in methanol. It is very slightly soluble in chloroform, and practically insoluble in ether and in solvent hexane.

Identification—Prepare a solution of Lanatoside C in methanol containing 2.5 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 5 µl. of this solution and 5 µl. of a methanol solution of NF Lanatoside C Reference Standard containing 2.5 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of benzene-methanol (4:1) until the solvent front has advanced about 10 cm. from the origin. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 10) in methanol and heating at about 140° for 5 minutes. Cool, and examine under ultraviolet light: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Specific rotation, page 822—The specific rotation at 20° of Lanatoside C, previously dried in vacuum over phosphorus pentoxide to constant weight, determined in a solution in methanol containing 200 mg. of Lanatoside C in each 10 ml., is between +32.0° and +34.5°.

Loss on drying, page 814—Dry Lanatoside C in vacuum over phosphorus pentoxide to constant weight: it loses not more than 7.5 percent of its weight.

Residue on ignition, page 858—Lanatoside C yields not more than 0.1 percent of residue on ignition.

Assay—

Standard preparation—Transfer about 25 mg. of NF Lanatoside C Reference Standard, accurately weighed, to a 500-ml. volumetric flask, add alcohol to volume, and mix.

Assay preparation—Transfer about 25 mg. of Lanatoside C, accurately weighed, to a 500-ml. volumetric flask, add alcohol to volume, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate glass-stoppered conical flasks. To a third flask add 5.0 ml. of alcohol to serve as the blank. To each flask add 3.0 ml. of alkaline picrate T.S., and mix by swirling, maintaining the temperature at 25 ± 3°. Allow the solutions to stand for 25 minutes protected from direct light. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 490 mµ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{49}H_{76}O_{20}$ in the Lanatoside C taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Lanatoside C in tight, light-resistant containers.

CATEGORY—Cardiotonic.

USUAL DOSE—Oral, Initial, **7.5–10.0 mg.** Maintenance, **0.5–1.5 mg.**

Lanatoside C Tablets

Lanatoside C Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{49}H_{76}O_{20}$.

Identification—Shake a portion of finely powdered Lanatoside C Tablets, equivalent to about 1 mg. of lanatoside C, with 10 ml. of water, and extract with 25 ml. of chloroform-alcohol (7:3). Evaporate the extract to dryness on a steam bath, and dissolve the residue in 0.4 ml. of methanol: a 5-μl. portion of the solution so obtained responds to the *Identification* test under *Lanatoside C*, page 389.

Disintegration, page 878—The disintegration time limit for Lanatoside C Tablets is 15 minutes.

Content uniformity, *Method I*, page 799—Lanatoside C Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Lanatoside C*, page 389.

Assay preparation—Weigh and finely powder not less than 20 Lanatoside C Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg. of Lanatoside C, to a 100-ml. volumetric flask, add 50 ml. of alcohol, and shake mechanically for 15 minutes, protecting the mixture from direct sunlight. Dilute to volume with alcohol, mix, and filter, discarding the first 20 ml. of filtrate.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Lanatoside C*, page 389. Calculate the quantity, in mg., of $C_{49}H_{76}O_{20}$ in the portion of the Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Lanatoside C Tablets in well-closed containers.

Tablets available—Lanatoside C Tablets usually available contain the following amount of Lanatoside C: 500 mcg.

CATEGORY and DOSE—See Lanatoside C.

Lavender Oil

Lavender Oil is the volatile oil distilled with steam from the fresh flowering tops of *Lavandula officinalis* Chaix ex Villars (*Lavandula vera* De Candolle) (Fam. *Labiatæ*). It contains not less than 35.0 percent of total esters calculated as $C_{12}H_{20}O_2$ (linalyl acetate).

Description—Lavender Oil is a colorless or yellow liquid, having the characteristic odor and taste of lavender flowers.

Solubility in 70 percent alcohol—One volume of Lavender Oil dissolves in 4 volumes of 70 percent alcohol.

Specific gravity, page 866—The specific gravity of Lavender Oil is not less than 0.875 and not more than 0.888.

Angular rotation, page 822—The angular rotation of Lavender Oil is between $-3°$ and $-10°$ in a 100-mm. tube.

Refractive index, page 858—The refractive index of Lavender Oil is not less than 1.459 and not more than 1.470 at 20°.

Alcohol—Shake 5 ml. of Lavender Oil with an equal volume of water in a narrow, graduated, glass-stoppered, 10-ml. cylinder: the volume of the oil does not diminish.

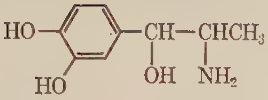
Foreign water-soluble esters—Shake 20.0 ml. of Lavender Oil with 40 ml. of 5 percent alcohol in a glass-stoppered, 100-ml. cylinder. When the mixture has cleared, pipet 30.0 ml. of the alcohol solution into a 125-ml. conical flask. Add phenolphthalein T.S., and neutralize the solution with 0.5 *N* sodium hydroxide. Add 5.0 ml. of 0.5 *N* sodium hydroxide, and heat the mixture on a steam bath under a reflux condenser for 1 hour. Allow the mixture to cool, and titrate the excess alkali with 0.5 *N* hydrochloric acid: not less than 4.7 ml. of the acid is required for neutralization.

Assay—Place about 5 g. of Lavender Oil, accurately weighed, in a 250-ml. conical flask, add 5 ml. of neutralized alcohol and 2 drops of phenolphthalein T.S., and add, dropwise, 0.1 *N* sodium hydroxide until a faint pink color appears. Add 50.0 ml. of 0.5 *N* alcoholic potassium hydroxide, connect the flask to a reflux condenser, and heat on a steam bath for 1 hour. Allow the mixture to cool, add 20 ml. of water, add phenolphthalein T.S., and titrate the excess alkali with 0.5 *N* hydrochloric acid. Perform a blank determination, disregarding the 0.1 *N* sodium hydroxide (see *Residual Titrations*, page 883). Each ml. of 0.5 *N* alcoholic potassium hydroxide consumed in the saponification is equivalent to 98.15 mg. of $C_{12}H_{20}O_2$.

Packaging and storage—Preserve Lavender Oil in tight containers.

CATEGORY—Perfume.

Levonordefrin



(−)-α-(1-Aminoethyl)-3,4-dihydroxybenzyl Alcohol

$C_9H_{13}NO_3$ Mol. wt. 183.21

Levonordefrin, dried in vacuum at 60° for 15 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_9H_{13}NO_3$.

Description—Levonordefrin occurs as a white to buff-colored, odorless, crystalline solid. It melts at about 210°.

Solubility—Levonordefrin is practically insoluble in water, and is slightly soluble in acetone, in chloroform, in alcohol, and in ether. It is freely soluble in aqueous solutions of mineral acids.

Identification—

A: Dissolve about 100 mg. of Levonordefrin in 10 ml. of water containing 2 drops of nitric acid and add 1 ml. of silver nitrate T.S.: the solution remains clear and does not change in color (*absence of chloride and distinction from the hydrochloride salt*).

B: Add 100 mg. of Levonordefrin to 2 ml. of a saturated solution of chloranil in acetone: the yellow solution turns reddish brown within 15 minutes (*presence of an amino group*).

C: To a suspension of about 100 mg. of Levonordefrin in 10 ml. of water add 1 drop of ferric chloride T.S.: the suspension immediately turns green and changes to deep blue within one minute. Add 2 drops of diluted hydrochloric acid: the color reverts to light green.

Specific rotation, page 822—The specific rotation of Levonordefrin, previously dried in vacuum at 60° for 15 hours, determined in a solution prepared by dissolving 500 mg. of Levonordefrin in 3 ml. of 1 *N* hydrochloric acid and diluting to 10.0 ml. with water, is not less than −28° and not more than −31°.

Loss on drying, page 814—Dry Levonordefrin in vacuum at 60° for 15 hours: it loses not more than 1 percent of its weight.

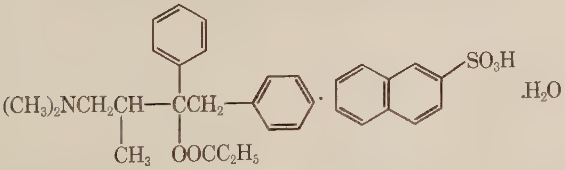
Residue on ignition, page 858—Levonordefrin yields not more than 0.2 percent of residue on ignition.

Assay—Transfer about 350 mg. of Levonordefrin, previously dried in vacuum at 60° for 15 hours and accurately weighed, to a small flask, dissolve it in 50 ml. of glacial acetic acid, heating if necessary, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 18.32 mg. of $C_9H_{13}NO_3$.

Packaging and storage—Preserve Levonordefrin in well-closed containers.

CATEGORY—Vasoconstrictor.

Levopropoxyphene Napsylate*



(−)-α-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol Propionate (ester) 2-Naphthalenesulfonate (salt)

$C_{22}H_{29}NO_2 . C_{10}H_8O_3S . H_2O$ Mol. wt. 565.73

Levopropoxyphene Napsylate contains not less than 97.0 percent and not more than 101.0 percent of $C_{22}H_{29}NO_2 . C_{10}H_8O_3S$, calculated on the anhydrous basis.

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* Patented. See notice, page ii.

Description—Levopropoxyphene Napsylate occurs as a white powder having essentially no odor but having a bitter taste.

Solubility—Levopropoxyphene Napsylate is soluble in methanol, in alcohol, in chloroform, and in acetone. It is very slightly soluble in water.

Melting range, page 814—Levopropoxyphene Napsylate, dried at 105° for 3 hours, melts within a range of 4° between 158° and 165°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Levopropoxyphene Napsylate, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Levopropoxyphene Napsylate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 25,000 solution of Levopropoxyphene Napsylate in methanol exhibits maxima and minima at the same wavelengths as that of NF Levopropoxyphene Napsylate Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis at the point of maximum absorption occurring at about 275 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Levopropoxyphene Napsylate, determined in a solution in chloroform containing 100 mg. of Levopropoxyphene Napsylate in each 10 ml. is between −35° and −43°.

X-ray diffraction, page 902—The X-ray diffraction pattern of Levopropoxyphene Napsylate conforms to the following pattern:

d	I/I_1
16.2	40
10.33	2
8.71	4
8.07	4
6.73	100
6.34	50
5.76	50
5.42	60
5.23	20
4.60	70
4.42	70
4.23	2
4.08	80
3.92	30
3.62	30
3.44	20
3.37	20
3.26	20
3.17	8
2.96	6
2.86	10
2.80	10
2.67	10
2.59	15
2.46	2
2.39	4
2.27	15
2.17	4
2.09	6
2.04	2
1.98	4
1.87	2
1.71	2
1.57	2

Water, page 900—Determine the water content of Levopropoxyphene Napsylate by the titrimetric method: not less than 2.5 percent and not more than 5 percent is found.

Residue on ignition, page 858—Levopropoxyphene Napsylate yields not more than 0.5 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Levopropoxyphene Napsylate is 30 parts per million.

Assay—Place a pledget of glass wool in the base of a 1 × 30-cm. ion-exchange column. Add to the column 15 ml. of a suitable anionic-exchange resin (page 907), and gently tamp the column to pack the resin. Pass 50 ml. of sodium hydroxide solution (1 in 4) through the column, adjusting the flow rate at about 2 to 4 ml. per minute, wash the column with water until the eluate is neutral, and then wash the column with 50 ml. of methanol, discarding the washings. (*Caution:* Do not permit the column to become dry at any time.) Before the last few ml. of methanol has passed through the column, place a 400-ml. beaker under the column, and pass through the column 25 ml. of a methanol solution containing about 550 mg. of Levopropoxyphene Napsylate, accurately weighed, collecting the eluate in the beaker. Wash the column with one 25-ml. portion and one 50-ml. portion of methanol, collecting the washings in the beaker. Add 50 ml. of water to the beaker, and titrate the combined eluates with 0.1 *N* hydrochloric acid, determining the end-point potentiometrically with suitable electrodes. Each ml. of 0.1 *N* hydrochloric acid is equivalent to 54.77 mg. of $C_{22}H_{29}NO_2 . C_{10}H_8O_3S$.

Packaging and storage—Preserve Levopropoxyphene Napsylate in tight containers.

CATEGORY—Antitussive.

USUAL DOSE—**50** to **100 mg.** every 4 hours.

Levopropoxyphene Napsylate Capsules

Levopropoxyphene Napsylate Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{29}NO_2$ (levopropoxyphene base).

Identification—

A: The solution prepared from Levopropoxyphene Napsylate Capsules as directed in the *Assay* exhibits an absorbance maximum at about 5.80 μ.

B: Transfer to a small flask the contents of Levopropoxyphene Napsylate Capsules, equivalent to about 100 mg. of levopropoxyphene base, mix with 10 ml. of chloroform, and filter: the solution is levorotatory (see page 822).

Content uniformity, *Method II*, page 798—Levopropoxyphene Napsylate Capsules meet the requirements of the content uniformity test for capsules, using the following special procedure: Quantitatively transfer the contents of a capsule as completely as possible to a 100-ml. volumetric flask. Rinse the empty capsule with methanol, and add these rinsings to the flask. Add 50 ml. of methanol, and shake mechanically for 15 minutes. Dilute to volume with methanol, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol to provide a solution containing approximately 25 mcg. of levopropoxyphene base per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Levopropoxyphene Napsylate Reference Standard, in the same medium, at a concentration of about 42 mcg. per ml., in 1-cm. cells, at the maximum at about 275 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{22}H_{29}NO_2$ in the capsule by the formula $(T/D) \times (0.6198C) \times (A_U/A_S)$, in which T is the labeled quantity of levopropoxyphene base, in mg., in the capsule; D is the exact concentration, in mcg. per ml., of levopropoxyphene base in the sample solution, based upon the labeled content per capsule and the extent of dilution; 0.6198 is the ratio of the molecular weight of levopropoxyphene base to that of anhydrous levopropoxyphene napsylate; C is the exact concentration of levopropoxyphene napsylate in the Reference Standard solution, in mcg. per ml., calculated on the anhydrous basis; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—

Standard preparation—Transfer about 85 mg. of NF Levopropoxyphene Napsylate Reference Standard, accurately weighed, to a 125-ml. separator containing 40 ml. of water, and proceed as directed under *Assay preparation*, beginning with "Extract with four 25-ml. portions of chloroform. . . ."

Assay preparation—Remove as completely as possible the contents of not less than 20 Levopropoxyphene Napsylate Capsules, and weigh. Transfer an accurately weighed portion of the contents, equivalent to about 50 mg. of levopropoxyphene base, to a 125-ml. separator containing 40 ml. of water. Extract with four 25-ml. portions of chloroform, and combine the chloroform extracts in a 250-ml. separator, discarding the aqueous phase. Add 40 ml. of 0.5 *N* sodium hydroxide to the chloroform, shake for 3 minutes, and allow the mixture to stand until the emulsion breaks. Filter the chloroform phase through a layer of anhydrous sodium sulfate into a 150-ml. beaker. Evaporate the chloroform solution to about 3 ml. on a steam bath with the aid of a current of air, and complete the evaporation of the remaining chloroform without further heat. With the aid of chloroform, quantitatively transfer the residue to a 10-ml. glass-stoppered flask, again evaporate the chloroform as before, and dissolve the last residue in 2.0 ml. of chloroform.

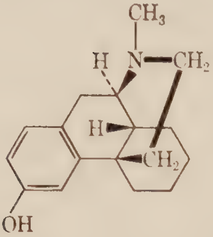
Procedure—Concomitantly determine the absorbance of each solution in 0.1-mm. cells, at the maximum at about 5.80 μ, with a suitable infrared spectrophotometer, using chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{29}NO_2$ in the portion of the Capsules taken by the formula $0.6198W \times (A_U/A_S)$, in which 0.6198 is the ratio of the molecular weight of levopropoxyphene base to that of anhydrous levopropoxyphene napsylate, and W is the exact weight, in mg., calculated on the anhydrous basis, of NF Levopropoxyphene Napsylate Reference Standard taken in the preparation of the *Standard preparation*.

Packaging and storage—Preserve Levopropoxyphene Napsylate Capsules in tight containers.

Capsules available—Levopropoxyphene Napsylate Capsules usually available contain the following amounts of levopropoxyphene base: 50 and 100 mg.

CATEGORY and DOSE—See Levopropoxyphene Napsylate.

Levorphanol Tartrate



$.H_2C_4H_4O_6.2H_2O$

17-Methylmorphinan-3-ol Tartrate (1:1)

$C_{17}H_{23}NO.C_4H_6O_6.2H_2O$ Mol. wt. 443.50

Levorphanol Tartrate, dried in vacuum at 90° to constant weight, contains not less than 99.0 percent and not more than 101.0 percent of $C_{17}H_{23}NO.C_4H_6O_6$.

Description—Levorphanol Tartrate occurs as a practically white, odorless, crystalline powder.

Solubility—Levorphanol Tartrate is sparingly soluble in water. It is slightly soluble in alcohol, and is insoluble in chloroform and in ether.

Identification—

A: Mix about 1 mg. of Levorphanol Tartrate with 1 ml. of a solution of ammonium molybdate in sulfuric acid (1 in 100): a blue or greenish blue color develops.

B: Dissolve about 5 mg. of Levorphanol Tartrate in 1 ml. of water, and add a drop of diluted hydrochloric acid and 2 drops of ferric chloride T.S.: no red color develops (*distinction from morphine*). Heat the mixture to boiling and add 1 ml. of potassium ferricyanide (1 in 200): an intense blue color develops.

C: Dissolve about 50 mg. of Levorphanol Tartrate in 2 ml. of diluted sulfuric acid, add 1 ml. of a freshly prepared solution of mercuric nitrate (700 mg. in 4 ml.) and 100 mg. of sodium nitrite, and filter the mixture: a red color develops immediately with heating.

Melting range, page 814—Levorphanol Tartrate melts between 114° and 117°.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 7500 solution of Levorphanol Tartrate in 0.1 *N* hydrochloric acid exhibits a maximum at 279 ± 2 mμ and a minimum at 246 ± 3 mμ.

Loss on drying, page 814—Dry Levorphanol Tartrate in vacuum at 90° to constant weight: it loses not less than 7 percent and not more than 9 percent of its weight.

Residue on ignition, page 858—Levorphanol Tartrate yields not more than 0.1 percent of residue on ignition.

Specific rotation, page 822—The specific rotation of Levorphanol Tartrate, determined in a solution in water containing 300 mg. in each 10 ml. is between −13.5° and −15.0°.

Assay—Transfer about 250 mg. of Levorphanol Tartrate, previously dried in vacuum at 90° to constant weight and accurately weighed, into a 250-ml. flask, add 25 ml. of dehydrated alcohol, and warm slightly to dissolve. Dilute the solution with 100 ml. of chloroform, add 4 drops of methanolic methyl red T.S., and titrate with 0.02 *N* perchloric acid in dioxane to a red end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.02 *N* perchloric acid is equivalent to 8.149 mg. of $C_{17}H_{23}NO.C_4H_6O_6$.

Packaging and storage—Preserve Levorphanol Tartrate in well-closed containers.

CATEGORY—Analgesic (narcotic).

USUAL DOSE—Oral and subcutaneous, **2 mg.**

USUAL DOSE RANGE—**1** to **3 mg.**

Levorphanol Tartrate Injection

Levorphanol Tartrate Injection is a sterile solution of levorphanol tartrate in water for injection. It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$.

Identification—

A: To 1 ml. of Levorphanol Tartrate Injection add 1 drop of diluted hydrochloric acid and 2 drops of ferric chloride T.S. Heat to boiling and add 1 ml. of potassium ferricyanide solution (1 in 200): a blue-green color develops.

B: The angular rotation of Levorphanol Tartrate Injection is levorotatory, page 822.

pH, page 824—The pH of Levorphanol Tartrate Injection is between 4.2 and 4.4.

Other requirements—Levorphanol Tartrate Injection meets the requirements under *Injections*, page 810.

Assay—Transfer to a 125-ml. separator 20.0 ml. of Levorphanol Tartrate Injection. Add 5 g. of sodium chloride and sufficient sodium bicarbonate to make the solution alkaline to litmus. Add an additional 100 mg. of sodium bicarbonate, and completely extract the levorphanol with successive portions of a mixture of 3 parts of ether and 1 part of chloroform. Collect the extracts in a 500-ml. conical flask, evaporate to about 30 ml., add 50 ml. of chloroform and 1 drop of methanolic methyl red T.S., and titrate with 0.01 N perchloric acid in dioxane to a red endpoint. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 N perchloric acid is equivalent to 4.435 mg. of $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$.

Packaging and storage—Preserve Levorphanol Tartrate Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Levorphanol Tartrate Injection usually available contains the following amounts of levorphanol tartrate: 2 mg. in 1 ml., and 20 mg. in 10 ml.

CATEGORY and DOSE—See Levorphanol Tartrate.

Levorphanol Tartrate Tablets

Levorphanol Tartrate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$.

Identification—

A: Finely powder a number of Levorphanol Tartrate Tablets. To a portion, equivalent to about 1 mg. of levorphanol tartrate, add 1 ml. of water, 1 drop of diluted hydrochloric acid, 2 drops of ferric chloride T.S., and heat to boiling. To the hot solution add 1 ml. of potassium ferricyanide solution (1 in 200): a bluish color develops.

B: Powder a number of Levorphanol Tartrate Tablets, equivalent to about 60 mg. of levorphanol tartrate, and transfer the mixture to a small separator. Add 10 ml. of water, dissolve as much of the powder as possible, add about 400 mg. of sodium bicarbonate and extract the mixture with a 50-ml. portion of chloroform. Evaporate the filtered chloroform extract to a small volume on a steam bath, then dilute to 10 ml. with chloroform and determine the angular rotation in a 200-mm. tube: the solution is levorotatory.

Disintegration, page 878—The disintegration time limit for Levorphanol Tartrate Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Levorphanol Tartrate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer a tablet to a glass-stoppered flask, add 25.0 ml. of 0.1 N hydrochloric acid, and allow the tablet to disintegrate. Shake well, and filter through a small filter paper, discarding the first portion of the filtrate. Dilute a portion of the filtrate quantitatively and stepwise, if necessary, to provide a solution containing 80 mcg. of levorphanol tartrate per ml. Concomitantly determine the absorbance of this solution and of a standard solution of NF Levorphanol Tartrate, in the same medium and a concentration of about 80 mcg. per ml., in 1-cm. cells, at the maximum at about 279 mμ, with a suitable spectrophotometer, using 0.1 N hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of levorphanol tartrate, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution, and A_S is the absorbance of the standard solution.

Assay—Weigh and finely powder not less than 20 Levorphanol Tartrate Tablets. Weigh accurately a portion of the powder, equivalent to about 40 mg. of levorphanol tartrate, and transfer it to a 125-ml. separator. Add 20 ml. of water and sufficient sodium bicarbonate to make the suspension alkaline to litmus, and then add an additional 100 mg. of sodium bicarbonate. Completely extract the suspension with successive portions of a mixture of 3 parts of ether and 1 part of chloroform. Filter the combined extracts into a 500-ml. conical flask, evaporate to about

30 ml., add 50 ml. of chloroform, 1 drop of methanolic methyl red T.S., and titrate with 0.01 *N* perchloric acid in dioxane to a red end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* perchloric acid is equivalent to 4.435 mg. of $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$.

Packaging and storage—Preserve Levorphanol Tartrate Tablets in well-closed containers.

Tablets available—Levorphanol Tartrate Tablets usually available contain the following amount of levorphanol tartrate: 2 mg.

CATEGORY and DOSE—See Levorphanol Tartrate.

Light Mineral Oil, page 461

Magaldrate*

Magaldrate is a chemical combination of aluminum hydroxide and magnesium hydroxide, corresponding to the approximate formula of $Al_2H_{14}Mg_4O_{14}.2H_2O$. It contains the equivalent of not less than 28.0 percent and not more than 39.0 percent of MgO (magnesium oxide), and the equivalent of not less than 17.0 percent and not more than 25.0 percent of Al_2O_3 (aluminum oxide).

Description—Magaldrate occurs as a white, odorless, crystalline powder.

Solubility—Magaldrate is insoluble in water and in alcohol. It is soluble in dilute solutions of mineral acids.

Identification—Dissolve about 600 mg. of Magaldrate in 20 ml. of diluted hydrochloric acid, add 3 drops of methyl red T.S. and about 30 ml. of water, and heat to boiling. Add ammonia T.S. until the color just changes to yellow, continue boiling for 2 minutes, and filter: the filtrate responds to the tests for *Magnesium,* page 809. Wash the precipitate with 50 ml. of hot ammonium chloride solution (1 in 50), then dissolve the precipitate in 15 ml. of diluted hydrochloric acid: the solution responds to the tests for *Aluminum,* page 807.

X-ray diffraction, page 902—The X-ray diffraction pattern of Magaldrate conforms to the following pattern:

d	I/I_1
2.57	95
2.30	55
1.97	33
1.52	100
1.49	65
1.41	10
1.31	10
1.265	12
0.992	6
0.973	8
0.876	10

Acid-consuming capacity—Transfer about 3 g. of Magaldrate, accurately weighed, to a 250-ml. beaker, add 100.0 ml. of 1 *N* hydrochloric acid, and stir until the solution becomes clear. Titrate the excess acid with 1 *N* sodium hydroxide to a pH of 3.0, determined potentiometrically: the volume of 1 *N* acid consumed is not less than 18.0 ml. for each g. of Magaldrate.

Loss on drying, page 814—Dry Magaldrate at 105° for 3 hours: it loses not more than 10 percent of its weight.

Soluble chloride—Boil 1 g. of Magaldrate, accurately weighed, with 50.0 ml. of water for 5 minutes, cool, add sufficient water to restore the original volume, mix, and filter. To 25.0 ml. of the filtrate add 0.1 ml. of potassium chromate T.S., and then titrate with 0.1 *N* silver nitrate until a persistent pink color is obtained: not more than 5.0 ml. of 0.1 *N* silver nitrate is required (3.5 percent).

Soluble sulfate, page 784—A 2.5-ml. portion of the filtrate obtained in the test for *Soluble chloride* shows no more sulfate than corresponds to 1.0 ml. of 0.02 *N* sulfuric acid (1.9 percent).

Sodium—Transfer 2 g. of Magaldrate, accurately weighed, to a 100-ml. volumetric flask, place in an ice bath, add 5 ml. of nitric acid, and swirl to dissolve. Allow to warm to room temperature, dilute to volume with water, and mix. Filter, if necessary, to obtain a clear solution. Dilute 10.0 ml. of the filtrate to 100.0 ml. with water: the emission intensity of this solution, determined with a suitable flame photometer at 589 mμ and corrected for background transmission at 580 mμ, is not greater than that produced by a standard containing 2.2 mcg. of Na per ml., similarly measured (0.11 percent).

Arsenic—A solution of 1.25 g. of Magaldrate in 20 ml. of diluted hydrochloric acid meets the requirements of the

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* Patented. See notice, page ii.

Arsenic Test, page 777 (8 parts per million As).

Heavy metals, page 806—Dissolve 400 mg. of Magaldrate in 10 ml. of diluted hydrochloric acid, filter if necessary to obtain a clear solution, and dilute with water to 25 ml.: the heavy metals limit for Magaldrate is 60 parts per million.

Assay for magnesium oxide—Dissolve about 100 mg. of Magaldrate, accurately weighed, in 3 ml. of 1 *N* hydrochloric acid, and dilute to about 200 ml. with water. Add, with stirring, 1 g. of ammonium chloride, 20 ml. of triethanolamine, 10 ml. of ammonia-ammonium chloride buffer T.S., and 0.1 ml. of eriochrome black T.S., and titrate with 0.05 *M* disodium ethylenediaminetetraacetate to a blue color. Perform a blank determination, and make any necessary correction. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 2.016 mg. of MgO.

Assay for aluminum oxide—Dissolve about 100 mg. of Magaldrate, accurately weighed, in 3 ml. of 1 *N* hydrochloric acid, and dilute to about 30 ml. with water. Add, with stirring, 25.0 ml. of 0.05 *M* disodium ethylenediaminetetraacetate, 20 ml. of acetic acid-ammonium acetate buffer T.S., 60 ml. of alcohol, and 2 ml. of dithizone T.S., and titrate with 0.05 *M* zinc sulfate to a bright rose-pink color. Perform a blank determination, and make any necessary correction. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 2.549 mg. of Al_2O_3.

Packaging and storage—Preserve Magaldrate in well-closed containers.

CATEGORY—Antacid.

USUAL DOSE—**400** to **800 mg.** of magaldrate as required, preferably taken between meals and at bedtime.

Magaldrate Oral Suspension

Magaldrate Oral Suspension contains the equivalent of not less than 2.5 percent and not more than 3.0 percent (w/w) of MgO (magnesium oxide), and the equivalent of not less than 1.5 percent and not more than 2.0 percent (w/w) of Al_2O_3 (aluminum oxide).

Identification—

A: Dissolve 10 g. of Magaldrate Oral Suspension in 20 ml. of diluted hydrochloric acid, dilute to about 50 ml. with water, add 3 drops of methyl red T.S., and continue as directed in the test for *Identification* under *Magaldrate,* page 396, beginning with "... and heat to boiling."

B: Evaporate to dryness on a steam bath a few ml. of Magaldrate Oral Suspension: the residue so obtained displays an X-ray diffraction pattern which conforms to that detailed in the test for *X-ray diffraction* under *Magaldrate,* page 396.

Acid-consuming capacity—Transfer about 40 g. of Magaldrate Oral Suspension, accurately weighed, to a 250-ml. beaker, add 100.0 ml. of 1 *N* hydrochloric acid, and stir until the solution becomes clear. Titrate the excess acid with 1 *N* sodium hydroxide to a pH of 3.0, determined potentiometrically: the volume of 1 *N* acid consumed is not less than 1.8 ml. and not more than 2.4 ml. per g. of Suspension.

Other requirements—Evaporate to dryness on a steam bath about 5 ml. of Magaldrate Oral Suspension: the residue so obtained meets the requirements of the tests for *Arsenic* and *Heavy metals* under *Magaldrate,* page 396.

Assay for magnesium oxide—Dissolve about 1.2 g. of Magaldrate Oral Suspension, accurately weighed, in a mixture of 3 ml. of 1 *N* hydrochloric acid and 10 ml. of water, and continue as directed in the *Assay for magnesium oxide* under *Magaldrate,* page 396, beginning with "... and dilute to about 200 ml. with water."

Assay for aluminum oxide—Dissolve about 1.2 g. of Magaldrate Oral Suspension, accurately weighed, in a mixture of 3 ml. of 1 *N* hydrochloric acid and 10 ml. of water, and continue as directed in the *Assay for aluminum oxide* under *Magaldrate,* page 396, beginning with "... and dilute to about 30 ml. with water."

Packaging and storage—Preserve Magaldrate Oral Suspension in tight containers.

CATEGORY and DOSE—See Magaldrate.

Magaldrate Tablets

Magaldrate Tablets contain the equivalent of not less than 130 mg. and not more than 160 mg. of MgO (magnesium oxide), and the equivalent of not less than 80 mg. and not more than 105 mg. of Al_2O_3 (aluminum oxide) per tablet.

Identification—Extract five finely powdered Magaldrate Tablets with three 100-ml. portions of water, and heat the insoluble material to dryness on a steam bath: the residue so obtained meets the requirements of the tests for *Identification* and *X-ray diffraction* under *Magaldrate,* page 396.

Disintegration, page 878—The disintegration time limit for Magaldrate Tablets labeled to be swallowed is 2 minutes.

Weight variation, page 901—Magaldrate Tablets meet the requirements of the weight variation test for tablets.

Acid-consuming capacity—Weigh and finely powder not less than 20 Magaldrate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 15 tablets, to a 200-ml. volumetric flask, add 100.0 ml. of 2 *N* hydrochloric acid, shake for 15 minutes, dilute to volume with water, and mix. Filter, and transfer 100.0 ml. of the filtrate to a 250-ml. beaker. Titrate the excess acid with 1 *N* sodium hydroxide to a pH of 3.0, determined potentiometrically: not less than 10.0 ml. and not more than 12.2 ml. of 1 *N* acid is consumed per tablet.

Assay for magnesium oxide—Weigh and finely powder not less than 20 Magaldrate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 2.5 tablets, to a 100-ml. volumetric flask, add 30 ml. of 1 *N* hydrochloric acid, shake for 15 minutes, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a 400-ml. beaker, and continue as directed in the *Assay for magnesium oxide* under *Magaldrate,* page 396, beginning with "... and dilute to about 200 ml. with water."

Assay for aluminum oxide—Weigh and finely powder not less than 20 Magaldrate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 2.5 tablets, to a 100-ml. volumetric flask, add 30 ml. of 1 *N* hydrochloric acid, shake for 15 minutes, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution and 20 ml. of water to a 250-ml. beaker, and continue as directed in the *Assay for aluminum oxide* under *Magaldrate,* page 396, beginning with "Add, with stirring, 25.0 ml. of 0.05 *M* disodium ethylenediaminetetraacetate . . . ."

Packaging and storage—Preserve Magaldrate Tablets in well-closed containers.

Labeling—Label Magaldrate Tablets to indicate whether they are to be swallowed or to be chewed.

CATEGORY and DOSE—See Magaldrate.

Magnesium Carbonate

Magnesium Carbonate is a basic hydrated magnesium carbonate or a normal hydrated magnesium carbonate. It contains the equivalent of not less than 40.0 percent and not more than 43.5 percent of MgO (magnesium oxide).

Description—Magnesium Carbonate occurs as light, white, friable masses, or as a bulky, white powder. It is odorless, and is stable in air.

Solubility—Magnesium Carbonate is practically insoluble in water, to which, however, it imparts a slightly alkaline reaction. It is insoluble in alcohol, but is dissolved by dilute acids with effervescence.

Identification—When Magnesium Carbonate is treated with diluted hydrochloric acid, it dissolves with effervescence and the resulting solution responds to the tests for *Magnesium,* page 809.

Soluble salts—Mix 2 g. of Magnesium Carbonate with 100 ml. of a mixture of equal volumes of 1-propanol and water. Heat the mixture to the boiling point with constant stirring, cool to room temperature, add water to make 100 ml., and filter. Evaporate 50 ml. of the filtrate on a steam bath to dryness, and dry at 105° for 1 hour: the weight of the residue does not exceed 10 mg. (1 percent).

Acid-insoluble substances—Mix 5 g. of Magnesium Carbonate with 75 ml. of water, add hydrochloric acid in small portions, with agitation, until no more of the Magnesium Carbonate dissolves, and boil for 5 minutes. If an insoluble residue remains, filter, wash well with water until the last washing is free from chloride, and ignite: the weight of the ignited residue does not exceed 2.5 mg. (0.05 percent).

Arsenic—A solution of 2.5 g. of Magnesium Carbonate in about 10 ml. of diluted hydrochloric acid meets the requirements of the *Arsenic Test,* page 777 (4 parts per million As).

Calcium oxide—Dissolve about 1 g. of Magnesium Carbonate, accurately weighed, in a mixture of 3 ml. of sulfuric acid and 22 ml. of water. Add 50 ml. of alcohol, and allow the mixture to stand overnight. If crystals of magnesium sulfate separate, warm the mixture to about 50° to dissolve them. Filter through a porcelain filter crucible containing an asbestos mat that previously has been washed with diluted sulfuric acid, water, and alcohol and ignited and weighed. Wash the crystals on the mat several times with a mixture of 2 volumes of alcohol and 1 volume of diluted sulfuric acid. Ignite the crucible and contents at a dull red heat, cool, and weigh. The weight of calcium sulfate so obtained, multiplied by 0.4119, gives the equivalent of CaO (calcium oxide) in the Magnesium Carbonate taken for the test: the CaO does not exceed 0.6 percent.

Heavy metals, page 806—Dissolve 1 g. of Magnesium Carbonate in 10 ml. of diluted hydrochloric acid, and evaporate the solution on a steam bath to dryness. Toward the end of the evaporation stir frequently to disintegrate the residue so that finally a dry powder is obtained. Dissolve the residue in 20 ml. of water, and evaporate to dryness in the same manner as before. Redissolve the residue in 20 ml. of water, filter if necessary, and add to the filtrate 2 ml. of diluted acetic acid and water to make 25 ml.: the heavy metals limit for Magnesium Carbonate is 30 parts per million.

Iron—Boil 100 mg. of Magnesium Carbonate with 5 ml. of a mixture of 1 volume of nitric acid and 9 volumes of water for 1 minute. Cool, dilute to 50 ml. with water, add about 50 mg. of ammonium persulfate and 5 ml. of ammonium thiocyanate T.S., mix, and transfer to a color-comparison tube. Treat in the same manner 2.0 ml. of a solution of ferric ammonium sulfate, made by dissolving 86.5 mg. of ferric ammonium sulfate in 10 ml. of diluted sulfuric acid and adding water to make 1000 ml., each ml. representing 0.01 mg. of Fe. The color of the test solution is not deeper than that of the solution containing the standard iron solution (0.02 percent).

Assay—Dissolve about 1 g. of Magnesium Carbonate, accurately weighed, in 30.0 ml. of 1 *N* sulfuric acid, add 3 drops of methyl orange T.S., and titrate the excess acid with 1 *N* sodium hydroxide. From the volume of 1 *N* sulfuric acid consumed, deduct the volume of 1 *N* sulfuric acid corresponding to the content of calcium oxide in the weight of Magnesium Carbonate taken for the assay. The difference is the volume of 1 *N* sulfuric acid equivalent to the magnesium oxide present. Each ml. of 1 *N* sulfuric acid is equivalent to 20.15 mg. of MgO and to 28.04 mg. of CaO.

Packaging and storage—Preserve Magnesium Carbonate in well-closed containers.

CATEGORY—Antacid.

USUAL DOSE RANGE—**500 mg. to 2 g.** four times a day.

Magnesium Citrate Solution

Magnesium Citrate Solution contains, in each 100 ml., an amount of magnesium citrate corresponding to not less than 1.55 g. and not more than 1.9 g. of MgO (magnesium oxide).

Magnesium Carbonate	**15 g.**
Anhydrous Citric Acid	**27.4 g.**
Syrup	**60 ml.**
Talc	**5 g.**
Lemon Oil	**0.1 ml.**
Potassium Bicarbonate	**2.5 g.**
Purified Water, a sufficient quantity,	
To make	**350 ml.**

NOTE: An amount of citric acid containing 1 molecule of water of hydration, equivalent to 27.4 g. of anhydrous citric acid, may be used in the above formula.

Dissolve the anhydrous citric acid in 150 ml. of hot purified water in a suitable dish, add slowly the magnesium carbonate, previously mixed with 100 ml. of purified water, and stir until it is dissolved. Then add the syrup, heat the mixed liquids to the boiling point, immediately add the lemon oil, previously triturated with the talc, and filter the mixture, while hot, into a strong bottle (previously rinsed with boiling purified water) of suitable capacity. Add enough boiled purified water to make the product measure 350 ml. Stopper the bottle with purified cotton, allow to cool, add the potassium bicarbonate, and immediately stopper the bottle securely. Lastly, shake the solution occasionally until the potassium bicarbonate is dissolved.

NOTE: In this process the 2.5 g. of potassium bicarbonate may be replaced by 2.1 g. of sodium bicarbonate, preferably in tablet form. The Solution may be further carbonated by the use of CO_2 under pressure.

The stability of Magnesium Citrate Solution may be improved by pasteurizing or sterilizing the Solution. For Solutions which are not intended to be pasteurized or sterilized, the stability may be improved by employing 30 g. of citric acid and a quantity of magnesium carbonate equivalent to 6.0 g. of MgO for each 350 ml. of Solution.

Description—Magnesium Citrate solution is a colorless to slightly yellow, clear, effervescent liquid, having a sweet, acidulous taste and a lemon flavor.

Identification—

A: Magnesium Citrate Solution responds to the tests for *Magnesium,* page 809.

B: To 5 ml. of Magnesium Citrate Solution add 1 ml. of potassium permanganate T.S. and 5 ml. of mercuric sulfate T.S., and heat the solution: a white precipitate is formed

Chloride, page 784—A 2-ml. portion of Magnesium Citrate Solution shows no more chloride than corresponds to 0.3 ml. of 0.02 *N* hydrochloric acid (0.01 percent).

Sulfate, page 784—A 2-ml. portion of Magnesium Citrate Solution shows no more sulfate than corresponds to 0.3 ml. of 0.02 *N* sulfuric acid (0.015 percent).

Tartaric acid—To 10 ml. of Magnesium Citrate Solution in a test tube add 1 ml. of glacial acetic acid and 3 ml. of a solution of potassium acetate (1 in 2), shake the mixture vigorously, then gently rub the inner wall of the test tube with a glass rod for a few minutes, and allow to stand for 1 hour: no white, crystalline precipitate soluble in ammonia T.S. is formed.

Assay for anhydrous citric acid—Measure accurately 10 ml. of Magnesium Citrate Solution, which has been previously freed from excessive carbon dioxide by repeated pouring, into a 250-ml. beaker, and add 30 ml. of water. Then add 3 drops of phenolphthalein T.S. and just enough 1 *N* sodium hydroxide to give the liquid a persistent pink color, and acidify with 4 drops of 1 *N* hydrochloric acid. Add 20 ml. of calcium chloride T.S., and concentrate, by boiling, to about 30 ml., stirring constantly with a rubber-tipped glass rod during the boiling. Completely transfer the precipitate from the hot mixture to a filter of from 9 to 11 cm. in diameter with the aid of small quantities of boiling water. Then wash the precipitate five times with boiling water. Collect the filtrate and washings in a 150-ml. beaker, and concentrate the solution, by boiling, to about 20 ml. Add sufficient ammonia T.S., dropwise, to give the liquid a distinct red color, and then concentrate to about 10 ml. Transfer the precipitate completely from the hot mixture to a filter of from 7 to 9 cm. in diameter with the aid of small quantities of boiling water, and wash the precipitate six times with 5-ml. portions of boiling water.

Dry the two filters with the precipitates, and incinerate them together in a loosely covered platinum crucible, heating at first at a low temperature until the precipitates are well charred, and then remove the cover and raise the temperature until the residue is nearly white. If a gas flame is used, it must not come in contact with the mass in the crucible. Cool, place the crucible with its contents in a suitable beaker, add about 30 ml. of water, and then 50.0 ml. of 0.5 *N* hydrochloric acid. When the residue has dissolved, remove the crucible, rinsing it well with water into the beaker. Add 100 ml. of water, cover the beaker with a watch glass, and boil gently for 10 minutes. Cool, and titrate the excess acid with 0.5 *N* sodium hydroxide, using phenolphthalein T.S. as the indicator. Not less than 23.7 ml. of 0.5 *N* hydrochloric acid is consumed (7.59 g. of anhydrous citric acid, $C_6H_8O_7$, in 100 ml. of the Solution).

Assay for magnesium oxide—Transfer to a 100-ml. volumetric flask 50.0 ml. of Magnesium Citrate Solution which has been previously freed from excessive carbon dioxide by repeated pouring. Add water to volume, and mix. Pipet 5.0 ml. of this solution to a beaker containing 150 ml. of water heated to 70° to 80°, add 1 ml. of ammonium chloride T.S., and then 3 ml. of stronger ammonia water. Mix thoroughly, and add slowly, with stirring, 8 ml. of 8-hydroxyquinoline T.S. After standing for 30 minutes, filter through a sintered-glass crucible, previously dried and weighed, and wash the precipitate with ten 10-ml. portions of water. Dry the crucible and contents at 105° for 3 hours, cool, and weigh. The weight of $C_{18}H_{12}MgN_2O_2 . 2H_2O$ so obtained, multiplied by 4.624, gives the equivalent of MgO in 100 ml. of the Solution.

Packaging and storage—Preserve Magnesium Citrate Solution in a cold place, preferably in a refrigerator, keeping the bottle on its side. Package Magnesium Citrate Solution in bottles containing not less than 200 ml.

CATEGORY—Cathartic.
USUAL DOSE—**200 ml.**

Magnesium Hydroxide

$Mg(OH)_2$ Mol. wt. 58.32

Magnesium Hydroxide, dried at 105° for 2 hours, contains not less than 95.0 percent and not more than 100.5 percent of $Mg(OH)_2$.

Description—Magnesium Hydroxide occurs as a bulky, white powder.

Solubility—Magnesium Hydroxide dissolves in dilute acids. It is practically insoluble in water and in alcohol.

Identification—A solution of Magnesium Hydroxide (1 in 20) in diluted hydrochloric acid responds to the tests for *Magnesium*, page 809.

Loss on drying, page 814—Dry Magnesium Hydroxide at 105° for 2 hours: it loses not more than 2 percent of its weight.

Loss on ignition—Transfer to a tared platinum crucible about 500 mg. of Magnesium Hydroxide, weigh accurately, and ignite at 800°, increasing the heat gradually, to constant weight: the loss in weight is not less than 30 percent and not more than 33 percent.

Soluble salts—Boil 2 g. of Magnesium Hydroxide with 100 ml. of water for 5 minutes in a covered beaker, then filter while hot. Titrate 50 ml. of the cooled filtrate with 0.1 *N* sulfuric acid using methyl red T.S. as the indicator: not more than 2 ml. of the acid is consumed. Evaporate 25 ml. of the filtrate to dryness, and dry at 105° for 3 hours: not more than 10 mg. of residue remains.

Carbonate—Boil a mixture of 100 mg. of Magnesium Hydroxide with 5 ml. of water, cool, and add 5 ml. of acetic acid: no effervescence is produced.

Arsenic—A solution of 1.25 g. of Magnesium Hydroxide in 20 ml. of diluted hydrochloric acid meets the requirements of the *Arsenic Test,* page 777 (8 parts per million As).

Calcium oxide—Dissolve about 500 mg. of Magnesium Hydroxide, accurately weighed, in a mixture of 3 ml. of sulfuric acid and 22 ml. of water. Add 50 ml. of alcohol, and allow the mixture to stand overnight. If crystals of magnesium sulfate separate, warm the mixture to about 50° to dissolve them. Filter through a tared porcelain filter crucible containing an asbestos mat which has been previously washed with diluted sulfuric acid, water, and alcohol, and ignited. Wash the crystals on the mat several times with a mixture of 3 volumes of alcohol and 1 volume of water. Ignite the crucible and contents at a dull red heat, cool, and weigh. The weight of calcium sulfate thus obtained, multiplied by 0.4119, gives the equivalent of CaO in the Magnesium Hydroxide taken for the test: the weight of CaO thus obtained does not exceed 1 percent.

Heavy metals, page 806—Dissolve 1 g. of Magnesium Hydroxide in 10 ml. of diluted hydrochloric acid and evaporate the solution to dryness on a steam bath. Toward the end of the evaporation, stir the residue frequently, disintegrate it so that finally a dry powder is obtained, dissolve the residue in 20 ml. of water, and filter. To the filtrate, which should be neutral to litmus, add 2 ml. of diluted acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Magnesium Hydroxide is 40 parts per million.

Assay—Transfer about 400 mg. of Magnesium Hydroxide, previously dried at 105° for 2 hours and accurately weighed, into a conical flask. Add 25.0 ml. of 1 *N* sulfuric acid, and after solution is complete add 3 drops of methyl red T.S. Titrate the excess acid with 1 *N* sodium hydroxide. From the volume of 1 *N* sulfuric acid, deduct the volume of 1 *N* sulfuric acid consumed, corresponding to the content of CaO in the Magnesium Hydroxide taken for the assay. The difference is the volume of 1 *N* sulfuric acid equivalent to the $Mg(OH)_2$ in the portion of Magnesium Hydroxide taken. Each ml. of 1 *N* sulfuric acid is equivalent to 29.16 mg. of $Mg(OH)_2$ and to 28.04 mg. of CaO.

Packaging and storage—Preserve Magnesium Hydroxide in tight containers.

CATEGORY—Antacid; cathartic.

USUAL DOSE RANGE—Antacid, **300** to **600 mg.**; cathartic, **2** to **4 g.**

Magnesium Phosphate

$Mg_3(PO_4)_2 . 5H_2O$ Mol. wt. 352.93

Magnesium Phosphate, ignited to constant weight, contains not less than 98.0 percent and not more than 101.5 percent of $Mg_3(PO_4)_2$.

Description—Magnesium Phosphate occurs as a white, odorless, and tasteless powder.

Solubility—Magnesium Phosphate is readily soluble in diluted mineral acids but is almost insoluble in water.

Identification—

A: Dissolve about 200 mg. of Magnesium Phosphate in 10 ml. of diluted nitric acid and add, dropwise, ammonium molybdate T.S.: a greenish yellow precipitate of ammonium phosphomolybdate forms which is soluble in ammonia T.S.

B: Dissolve 100 mg. of Magnesium Phosphate in 0.7 ml. of diluted acetic acid and 20 ml. of water. Add 1 ml. of ferric chloride T.S., let stand 5 minutes, and filter. Five ml. of the filtrate responds to the test for *Magnesium*, page 809.

Loss on ignition—Weigh accurately about 1 g. of Magnesium Phosphate and ignite at 425° to constant weight: it loses not less than 20 percent and not more than 27 percent of its weight.

Acid-insoluble substances—If an insoluble residue remains in the test for *Carbonate*, filter the solution, wash well with hot water until the last washing is free from chloride, and ignite the residue: the weight of the residue does not exceed 4 mg. (0.2 percent).

Soluble substances—Digest 2 g. of Magnesium Phosphate with 100 ml. of water for 30 minutes on a steam bath, cool, add sufficient water to restore the original volume, mix, and filter. Evaporate 50 ml. of the filtrate to dryness, and ignite gently to constant weight: the weight of the residue does not exceed 15 mg. (1.5 percent).

Carbonate—Mix 2 g. of Magnesium Phosphate with 20 ml. of water, and add hydrochloric acid, dropwise, to effect solution: no effervescence occurs when the acid is added.

Chloride, page 784—Dissolve 500 mg. of Magnesium Phosphate in 50 ml. of diluted nitric acid and add 1 ml. of silver nitrate T.S.: the turbidity does not exceed that produced by 1 ml. of 0.02 *N* hydrochloric acid (0.14 percent).

Nitrate—Mix 200 mg. of Magnesium Phosphate with 5 ml. of water, and add just sufficient hydrochloric acid to effect solution. Dilute with water to 10 ml., add 0.1 ml. of indigo carmine T.S., then add, with stirring, 10 ml. of sulfuric acid: the blue color persists for at least 5 minutes.

Sulfate, page 784—Dissolve 500 mg. of Magnesium Phosphate in the smallest possible amount of diluted hydrochloric acid, dilute to 48 ml. with water, and add 2 ml. of barium chloride T.S.: the turbidity does not exceed that produced by 3 ml. of 0.02 *N* sulfuric acid (0.6 percent).

Arsenic—A solution of 1.25 g. of Magnesium Phosphate in just sufficient diluted hydrochloric acid (about 9 ml.) to dissolve the sample meets the requirements of the *Arsenic Test*, page 777 (8 parts per million As).

Barium—Mix 2 g. of Magnesium Phosphate with 40 ml. of water, heat, add hydrochloric acid, dropwise, to effect solution, then add 1 ml. of acid in excess. Cool, dilute with water to 50 ml., and filter. To 5 ml. of the filtrate add 1 ml. of potassium sulfate T.S.: no turbidity is produced within 15 minutes.

Calcium—Mix 500 mg. of Magnesium Phosphate with 15 ml. of water, heat, and add sufficient hydrochloric acid, in small portions, to effect solution. Cool, add ammonia T.S., in small portions, to produce a slight permanent precipitate, then add 2 ml. of acetic acid. Dilute with water to 25 ml., and filter. To 10 ml. of the filtrate add 2 ml. of ammonium oxalate T.S.: not more than a slight turbidity is produced within 5 minutes.

Heavy metals, page 806—Dissolve 1 g. of Magnesium Phosphate in 4.5 ml. of diluted hydrochloric acid, and dilute to 25 ml. with water. The heavy metals limit for Magnesium Phosphate is 30 parts per million.

Dibasic salt and magnesium oxide—Ignite about 2.5 g. of Magnesium Phosphate to constant weight. Weigh accurately about 2 g. of the ignited salt, and dissolve it by warming with 50.0 ml. of 1 *N* hydrochloric acid. Cool, add 1 or 2 drops of methyl orange T.S., and slowly titrate the excess of 1 *N* hydrochloric acid with 1 *N* sodium hydroxide to a yellow color, vigorously shaking the mixture during the titration. Not less than 14.8 ml. and not more than 15.4 ml. of 1 *N* hydrochloric acid is consumed for each g. of the ignited salt.

Assay—Weigh accurately about 200 mg. of Magnesium Phosphate, previously ignited to constant weight, and dissolve it in a mixture of 25 ml. of water and 10 ml. of diluted nitric acid. Filter, if necessary, wash any precipitate, add sufficient ammonia T.S. to the filtrate to produce a slight precipitate, then dissolve the precipitate by the addition of 1 ml. of diluted nitric acid. Adjust the temperature to about 50°, add 75 ml. of ammonium molybdate T.S., and maintain the temperature at about 50° for 30 minutes, stirring occasionally. Wash the precipitate once or twice with water by decantation, using from 30 to 40 ml. each time and passing the washings through a filter. Transfer the precipitate to the filter, and wash with potassium nitrate solution (1 in 100) until the last washing is not acid to litmus paper. Transfer the precipitate and filter to the precipitation vessel, add 50 ml. of water and 40.0 ml. of 1 *N* sodium hydroxide, agitate until the precipitate is dissolved, add 3 drops of phenolphthalein T.S., and then titrate the excess alkali with

1 *N* sulfuric acid. Each ml. of 1 *N* sodium hydroxide is equivalent to 5.716 mg. of $Mg_3(PO_4)_2$.

Packaging and storage—Preserve Magnesium Phosphate in well-closed containers.

CATEGORY—Antacid.

USUAL DOSE—**1 g.**

Menadiol Sodium Diphosphate Tablets

Menadiol Sodium Diphosphate Tablets contain not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_8Na_4O_8P_2 . 6H_2O$.

Identification—

A: Triturate a quantity of powdered Menadiol Sodium Diphosphate Tablets, equivalent to about 100 mg. of menadiol sodium diphosphate, with a mixture of 10 ml. of water and 10 ml. of diluted sulfuric acid, centrifuge the mixture, and filter the supernatant liquid. To the filtrate add 1 ml. of 0.5 *N* ceric sulfate, mix, extract with 10 ml. of chloroform, and centrifuge. Evaporate the chloroform extract on a steam bath just to dryness, and then dry at 80° for 1 hour: the menadione so obtained melts between 103° and 107°, page 814.

B: To 50 mg. of the menadione obtained in *Identification test A* add 5 ml. of water, then add 75 mg. of sodium bisulfite, and heat on a steam bath, shaking vigorously until the substance is dissolved and the solution is almost colorless. Add water to make 50 ml., and mix. To 2 ml. of the solution add 2 ml. of alcoholic ammonia (prepared by mixing equal volumes of alcohol and stronger ammonia water), shake, and add 3 drops of ethyl cyanoacetate: a deep purplish blue color is produced, which, on the addition of 1 ml. of sodium hydroxide solution (1 in 3), changes to green and then to yellow.

C: Triturate a quantity of powdered Menadiol Sodium Diphosphate Tablets, equivalent to about 20 mg. of menadiol sodium diphosphate, with 10 ml. of water, centrifuge the mixture, filter the supernatant liquid, and evaporate to a volume of about 2 ml. Add 2 drops of nitric acid and 1 ml. of sulfuric acid, and heat slowly to the evolution of white fumes. Cool, cautiously dilute with water to about 10 ml., and filter if not clear. Render the filtrate slightly alkaline to litmus paper with ammonia T.S., then make it acid with nitric acid, and add to the warm solution 3 ml. of ammonium molybdate T.S.: a yellow precipitate is formed within a few minutes.

Disintegration, page 878—The disintegration time limit for Menadiol Sodium Diphosphate Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Menadiol Sodium Diphosphate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: [NOTE—Use low-actinic glassware.] Quantitatively transfer a finely powdered tablet to a glass-stoppered centrifuge tube, add 25 ml. of pH 8.0 phosphate buffer (see page 783), and shake vigorously for several minutes. Filter into a 50-ml. volumetric flask, rinse the centrifuge tube and filter with three 5-ml. portions of pH 8.0 phosphate buffer, adding the rinsings to the volumetric flask, dilute to volume with pH 8.0 phosphate buffer, and mix. Dilute a portion of this solution quantitatively and stepwise, if necessary, with pH 8.0 phosphate buffer to provide a solution containing approximately 40 mcg. of menadiol sodium diphosphate per ml. Concomitantly determine the absorbance of this solution and of a solution of USP Menadiol Sodium Diphosphate, previously dried in vacuum over phosphorus pentoxide for 4 hours, in the same medium, at a concentration of about 40 mcg. per ml., at the maximum at about 297 mμ, with a suitable spectrophotometer, using pH 8.0 phosphate buffer as the blank. Calculate the quantity, in mg., of $C_{11}H_8Na_4O_8P_2 . 6H_2O$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of menadiol sodium diphosphate, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of menadiol sodium diphosphate in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of $C_{11}H_8Na_4O_8P_2 . 6H_2O$ in the standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution, and A_S is the absorbance of the standard solution.

Assay—Weigh and finely powder not less than 20 Menadiol Sodium Diphosphate Tablets. Weigh accurately into a 250-ml. beaker a portion of the powder, equivalent to about 50 mg. of menadiol sodium diphosphate. Moisten the powder with a few ml. of glacial acetic acid, then add sufficient of the acid to make 25 ml. Add 25 ml. of diluted hydrochloric acid and 25 ml. of water, mix, and titrate with 0.01 *N* ceric sulfate, determining the endpoint potentiometrically using a platinum-calomel electrode system. Each ml. of 0.01 *N* ceric sulfate is equivalent to 2.651 mg. of $C_{11}H_8Na_4O_8P_2 . 6H_2O$.

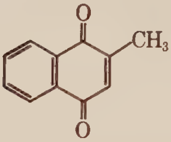
Packaging and storage—Preserve Menadiol Sodium Diphosphate Tablets in well-closed, light-resistant containers.

Tablets available—Menadiol Sodium Diphosphate Tablets usually available contain the following amount of menadiol sodium diphosphate: 5 mg.

CATEGORY—Source of Vitamin K.

USUAL DOSE OF MENADIOL SODIUM DIPHOSPHATE—**5 mg.** daily.

Menadione



2-Methyl-1,4-naphthoquinone

$C_{11}H_8O_2$ Mol. wt. 172.19

Menadione contains not less than 98.5 percent and not more than 101.0 percent of $C_{11}H_8O_2$, calculated on the dried basis.

Caution—Menadione powder is irritating to the respiratory tract and to the skin, and a solution of it in alcohol is a vesicant.

Description—Menadione occurs as a bright yellow, crystalline powder, and is nearly odorless. It is affected by sunlight.

Solubility—Menadione is practically insoluble in water. It is soluble in benzene and vegetable oils, and is sparingly soluble in chloroform and in alcohol.

Identification—To 50 mg. of Menadione add 5 ml. of water, then add 75 mg. of sodium bisulfite, and heat on a steam bath, shaking vigorously until the sample is dissolved and the solution is almost colorless. Dilute to 50 ml. with water, and mix. To 2 ml. of this solution add 2 ml. of alcoholic ammonia (prepared by mixing equal volumes of alcohol and stronger ammonia water), shake, and add 3 drops of ethyl cyanoacetate: a deep purplish blue color is produced, and on the addition of 1 ml. of sodium hydroxide solution (1 in 3), it changes to green and then to yellow.

Melting range, page 814—Menadione melts between 105° and 107°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Menadione, previously dried over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Menadione Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Menadione in alcohol exhibits maxima and minima at the same wavelengths as that of NF Menadione Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 250 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Menadione over silica gel for 4 hours: it loses not more than 0.3 percent of its weight.

Residue on ignition, page 858—Menadione yields not more than 0.1 percent of residue on ignition.

Assay—Weigh accurately about 150 mg. of Menadione, and transfer to a 150-ml. flask. Add 15 ml. of glacial acetic acid and 15 ml. of diluted hydrochloric acid, and rotate the flask until the Menadione is dissolved. Then add about 3 g. of zinc dust, close the flask with a stopper bearing a Bunsen valve, shake well, and allow to stand in the dark for 1 hour, with frequent shaking. Rapidly decant the solution through a pledget of cotton into another flask, immediately wash the reduction flask with three 10-ml. portions of freshly boiled and cooled water, add 0.1 ml. of orthophenanthroline T.S., and immediately titrate the combined filtrate and washings with 0.1 *N* ceric sulfate. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* ceric sulfate is equivalent to 8.609 mg. of $C_{11}H_8O_2$.

Packaging and storage—Preserve Menadione in well-closed, light-resistant containers.

CATEGORY—Vitamin K supplement.

USUAL DOSE—Oral and parenteral, **2 mg.** daily.

USUAL DOSE RANGE—**2** to **5 mg.**

Menadione Injection

Menadione Injection is a sterile solution of menadione in oil. It contains not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{11}H_8O_2$.

Other requirements—Menadione Injection meets the requirements under *Injections*, page 810.

Assay—

Standard preparation—Weigh accurately 25.0 mg. of NF Menadione Reference Standard, previously dried over phosphorus pentoxide for 4 hours in the dark, dissolve it in a mixture of equal volumes of alcohol and ether to make 100.0 ml., and mix. Keep the solution tightly closed in a dark, cool place, and use it within 7 days.

Assay preparation—Dilute an accurately measured volume of Menadione Injection, equivalent to about 25 mg. of menadione, with a mixture of equal volumes of ether and of alcohol to make 100.0 ml.

Procedure—Pipet 1.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate 50-ml. volumetric flasks, add to each 4 ml. of alcohol, and mix. Then to each flask add 1.0 ml. of a solution made by dissolving 50 mg. of 2,4-dinitrophenylhydrazine in 20 ml. of a mixture of 2 volumes of diluted hydrochloric acid and 1 volume of water. Place the flasks in a bath maintained at 70° to 75° for 15 minutes, shaking vigorously every 2 or 3 minutes. Immediately after the heating, cool the flasks to about 25°, then add to each 5 ml. of alcoholic ammonia, made by mixing equal volumes of alcohol and of stronger ammonia water. Shake the flasks thoroughly, add alcohol to make 50.0 ml., mix, allow to stand for 15 minutes, and decant from any separated oil. Determine the absorbance of each solution in a suitable spectrophotometer at 635 mμ relative to a reagent blank. Record the absorbance of the solution from the *Standard preparation* as A_S, and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{11}H_8O_2$ in the volume of the Injection taken by the formula $25 \times (A_U/A_S)$.

Packaging and storage—Preserve Menadione Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Menadione Injection usually available contains the following amounts of menadione: 2 and 5 mg. in 1 ml.

CATEGORY and DOSE—See Menadione.

Menadione Tablets

Menadione Tablets contain not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_8O_2$.

Identification—Powder a sufficient number of Menadione Tablets to yield about 10 mg. of menadione. Macerate the powder with two 10-ml. portions of chloroform, and decant the chloroform solution through a filter. Protect from light and evaporate the chloroform extract with the aid of a current of air to dryness. To 5 mg. of the residue add 1 ml. of water and 7.5 mg. of sodium bisulfite, and heat on a steam bath, shaking vigorously until the menadione is dissolved and the solution is nearly colorless. Dilute to 5 ml. with water, and mix. To 2 ml. of the solution add 2 ml. of alcoholic ammonia (prepared by mixing equal volumes of alcohol and stronger ammonia water), shake, and add 3 drops of ethyl cyanoacetate: a deep purplish blue color is produced, and on the addition of 1 ml. of sodium hydroxide solution (1 in 3), it changes to green and then to yellow.

Disintegration, page 878—The disintegration time limit for Menadione Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Menadione Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer one tablet to a 50-ml. volumetric flask containing 25 ml. of alcohol, and shake the flask until the tablet is dissolved. Dilute to volume with alcohol, mix, and filter, discarding the first 10 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise with alcohol to provide a solution containing approximately 5 mcg. of menadione per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Menadione Reference Standard, in the same medium at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 250 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{11}H_8O_2$ in the Tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of menadione in the tablet; D is the exact concentration, in mcg. per ml., of menadione in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Menadione Tablets. Weigh accurately a portion of the powder, equivalent to about 20 mg. of menadione, and transfer to a suitable vessel. Extract with three 10-ml. portions of chloroform, each time stirring the mixture well, then allowing the undissolved matter to settle and decanting the supernatant liquid onto a sintered-glass filter, suitably protected from light. Finally transfer the residue to the filter with the aid of chloroform, and wash it, the vessel and the filter with 5-ml. portions of chloroform until the last washing is colorless. Protect from light and evaporate the combined chloroform extracts and washings with the aid of a current of air to dryness. Add to the residue 7 ml. of glacial acetic acid, agitate until dissolved, then add 10 ml. of diluted hydrochloric acid and about 1 g. of zinc dust, with shaking. Close the flask with a stopper bearing a Bunsen valve, and allow to stand in the dark, with frequent shaking, for 1 hour, or until the solution is colorless. Rapidly decant the liquid through a pledget of cotton into another flask, wash the flask in which the reduction was made, and the filter with three 5-ml. portions of freshly boiled and cooled water, add 0.1 ml. of orthophenanthroline T.S., and promptly titrate the combined filtrate and washings with 0.02 *N* ceric sulfate. Perform a blank determination, and make any necessary correction. Each ml. of 0.02 *N* ceric sulfate is equivalent to 1.722 mg. of $C_{11}H_8O_2$.

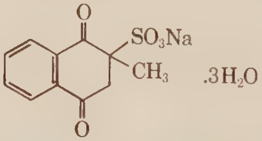
If the Tablets contain stearic acid, proceed as follows: Shake the chloroform extract of the Tablets, obtained as described in the preceding paragraph, in a separator with a mixture of 2 ml. of 1 *N* sodium hydroxide and 8 ml. of water, allow to separate, and drain the chloroform layer into a filter moistened with chloroform. Wash the water layer with 10 ml. of chloroform, and add the latter to the main chloroform solution. Finally wash the filter with about 10 ml. of chloroform, and proceed as directed in the foregoing paragraph, beginning with "Protect from light. . . ."

Packaging and storage—Preserve Menadione Tablets in well-closed containers.

Tablets available—Menadione Tablets usually available contain the following amounts of Menadione: 2, 5, and 10 mg.

CATEGORY and DOSE—See Menadione.

Menadione Sodium Bisulfite



Sodium 1,2,3,4-Tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonate

$C_{11}H_9NaO_5S.3H_2O$ Mol. wt. 330.29

Menadione Sodium Bisulfite, dried in vacuum at 100° for 3 hours, contains not less than 94.0 percent and not more than 100.5 percent of $C_{11}H_9NaO_5S$.

Description—Menadione Sodium Bisulfite occurs as a white, crystalline, odorless, hygroscopic powder.

Solubility—Menadione Sodium Bisulfite is freely soluble in water. It is slightly soluble in alcohol, and is practically insoluble in ether and in benzene.

Identification—

A: Dissolve about 100 mg. of Menadione Sodium Bisulfite in 10 ml. of water in a separator. Add 3 ml. of sodium hydroxide T.S., and extract the precipitated menadione with two 5-ml. portions of chloroform. Filter the chloroform solution through a chloroform-washed filter, and evaporate the filtrate with the aid of a current of air to dryness. Dissolve the residue in a few ml. of alcohol, and again evaporate to dryness: the menadione so obtained melts between 104° and 107°, page 814.

B: To 50 mg. of the menadione obtained in *Identification test A* add 5 ml. of water, then add 75 mg. of sodium bisulfite, and heat on a steam bath, shaking vigorously until the substance is dissolved and the solution is almost colorless. Add water to make 50 ml., and mix. To 2 ml. of the solution add 2 ml. of alcoholic ammonia (prepared by mixing equal volumes of alcohol and stronger ammonia water), shake, and add 3 drops of ethyl cyanoacetate: a deep purplish blue color is produced, which, on the addition of 1 ml. of sodium hydroxide solution (1 in 3), changes to green and then to yellow.

C: To 2 ml. of a solution of Menadione Sodium Bisulfite (1 in 25) add a few drops of diluted hydrochloric acid, and warm: sulfur dioxide, recognizable by its odor, is evolved.

Loss on drying, page 814—Dry Menadione Sodium Bisulfite at 100° in vacuum for 3 hours: it loses not less than 11 percent and not more than 16.5 percent of its weight.

Selenium—A *Test Preparation* prepared with 200 mg. of Menadione Sodium Bisulfite meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Assay—Dissolve about 300 mg. of Menadione Sodium Bisulfite, previously dried in vacuum at 100° for 3 hours and accurately weighed, in 20 ml. of water in a separator. Add 40 ml. of chloroform and 5 ml. of sodium carbonate T.S., and shake for about 30 seconds. Allow the layers to separate, and filter the chloroform extract through chloroform-moistened paper into a 250-ml. flask. Extract the water layer with two 40-ml. portions of chloroform, and filter as before, collecting the filtrate in the flask. Evaporate the combined chloroform extract to dryness in a water bath with the aid of a current of air. Add 15 ml. of glacial acetic acid and 15 ml. of diluted hydrochloric acid, and rotate the flask until the menadione is dissolved. Then add about 3 g. of zinc dust, close the flask with a stopper bearing a Bunsen valve, shake well, and allow to stand in the dark for 1 hour, with frequent shaking. Rapidly decant the solution through a pledget of cotton into another flask, immediately wash the reduction flask with three 10-ml. portions of carbon dioxide-free water, add 0.1 ml. of orthophenanthroline T.S., and at once titrate the combined filtrate and washings with 0.1 *N* ceric sulfate. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* ceric sulfate is equivalent to 13.81 mg. of $C_{11}H_9NaO_5S$.

Packaging and storage—Preserve Menadione Sodium Bisulfite in tight, light-resistant containers.

CATEGORY—Form of vitamin K.

USUAL DOSE—Intravenous and subcutaneous, **2 mg.** daily.

Menadione Sodium Bisulfite Injection

Menadione Sodium Bisulfite Injection is a sterile solution of menadione sodium bisulfite in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_9NaO_5S.3H_2O$.

Identification—

A: To a volume of Menadione Sodium Bisulfite Injection, equivalent to about 100 mg. of menadione sodium bisulfite, contained in a separator, add 3 ml. of sodium hydroxide T.S., and extract with two 10-ml. portions of chloroform. Filter the chloroform solution through a chloroform-washed filter, and evaporate the filtrate with the aid of a current of air to dryness. Dissolve the residue in a few ml. of alcohol, and again evaporate to dryness: the menadione so obtained melts between 103° and 107°, page 814.

B: A 50-mg. portion of the menadione obtained in *Identification test A* responds to *Identification test B* under *Menadione Sodium Bisulfite,* page 406.

C: To about 1 ml. of Menadione Sodium Bisulfite Injection add 2 to 3 drops of diluted hydrochloric acid, and warm: sulfur dioxide, recognizable by its odor, is evolved.

pH, page 824—The pH of Menadione Sodium Bisulfite Injection is between 2.0 and 4.0.

Other requirements—Menadione Sodium Bisulfite Injection meets the requirements under *Injections,* page 810.

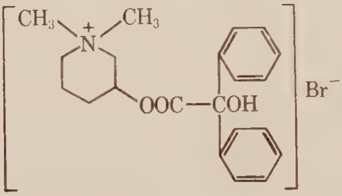
Assay—Transfer to a small separator an accurately measured volume of Menadione Sodium Bisulfite Injection, equivalent to about 50 mg. of menadione sodium bisulfite. Add 25 ml. of chloroform and 5 ml. of sodium carbonate T.S., and shake for about 30 seconds. Allow the layers to separate, and filter the chloroform extract through chloroform-moistened paper into a 125-ml. flask. Extract the water layer with two 25-ml. portions of chloroform, and filter as before, collecting the extracts in the flask. Evaporate the combined chloroform extracts to dryness in a water bath with the aid of a current of air. Add to the residue 7 ml. of glacial acetic acid, agitate until dissolved, then add 10 ml. of diluted hydrochloric acid and about 1 g. of zinc dust, with shaking. Close the flask with a stopper bearing a Bunsen valve, and allow to stand in the dark, with frequent shaking, for 1 hour, or until the solution is colorless. Rapidly decant the liquid through a pledget of cotton into another flask, wash the flask in which the reduction was made and the filter with three 5-ml. portions of carbon dioxide-free water, add 0.1 ml. of orthophenanthroline T.S., and at once titrate the combined filtrate and washings with 0.02 *N* ceric sulfate. Perform a blank determination, and make any necessary correction. Each ml. of 0.02 *N* ceric sulfate is equivalent to 3.303 mg. of $C_{11}H_9NaO_5S.3H_2O$.

Packaging and storage—Preserve Menadione Sodium Bisulfite Injection in single-dose, light-resistant containers, preferably of Type I glass.

Injections available—Menadione Sodium Bisulfite Injection usually available contains the following amounts of menadione sodium bisulfite: 2.5 mg. in 0.5 ml., 5 and 10 mg. in 1 ml., and 72 mg. in 10 ml.

CATEGORY and DOSE—See Menadione Sodium Bisulfite.

Mepenzolate Bromide*



3-Hydroxy-1,1-dimethylpiperidinium Bromide Benzilate

$C_{21}H_{26}BrNO_3$ Mol. wt. 420.35

Mepenzolate Bromide contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{26}BrNO_3$, calculated on the dried basis.

Description—Mepenzolate Bromide occurs as a white or light cream colored powder.

Solubility—Mepenzolate Bromide is freely soluble in methanol. It is slightly soluble in water and in chloroform, and is practically insoluble in ether.

Identification—

A: A solution of Mepenzolate Bromide responds to the tests for *Bromide*, page 808.

B: Dissolve 5 to 10 mg. of Mepenzolate Bromide in sulfuric acid: a bright yellow color is produced which changes to orange-red upon heating and is completely destroyed by dilution with several volumes of water.

Melting range, *Class Ia,* page 815—Mepenzolate Bromide melts between 230° and 237°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Mepenzolate Bromide, previously dried in vacuum at 80° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Mepenzolate Bromide Reference Standard, similarly measured.

Loss on drying, page 814—Dry Mepenzolate Bromide in vacuum at 80° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Mepenzolate Bromide yields not more than 0.2 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Mepenzolate Bromide in 23 ml. of water with heating, and add 2 ml. of diluted acetic acid: the heavy metals limit for Mepenzolate Bromide is 20 parts per million.

Bromide content—Dissolve about 250 mg. of Mepenzolate Bromide, accurately weighed, in about 100 ml. of water, add 2 ml. of nitric acid, and titrate with 0.1 *N* silver nitrate, determining the end-point potentiometrically using silver and silver chloride electrodes. Each ml. of 0.1 *N* silver nitrate is equivalent to 7.991 mg. of Br. Not less than 18.6 percent and not more than 19.4 percent of Br is found.

Assay—Dissolve about 350 mg. of Mepenzolate Bromide, accurately weighed, in 100 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 42.04 mg. of $C_{21}H_{26}BrNO_3$.

Packaging and storage—Preserve Mepenzolate Bromide in tight containers.

CATEGORY—Anticholinergic.
USUAL DOSE—**25 mg.** four times a day.
USUAL DOSE RANGE—**25** to **50 mg.**

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* Patented. See notice, page ii.

Mepenzolate Bromide Tablets

Mepenzolate Bromide Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{21}H_{26}BrNO_3$.

Identification—Powder a number of Mepenzolate Bromide Tablets, equivalent to about 100 mg. of mepenzolate bromide, digest with 50 ml. of chloroform for 10 minutes, cool, and filter.

A: Evaporate 5 ml. of the filtrate in a beaker, take up the residue in 10 ml. of water, and filter: the filtrate responds to the tests for *Bromide*, page 808.

B: Evaporate 5 ml. of the filtrate in a beaker, and add about 1 ml. of sulfuric acid: a bright yellow color is produced immediately which changes to orange-red upon warming and completely disappears when the solution is diluted with several volumes of water.

Disintegration, page 878—The disintegration time limit for Mepenzolate Bromide Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Mepenzolate Bromide Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Dissolve 100 mg. of NF Mepenzolate Bromide Reference Standard, previously dried at 80° for 3 hours and accurately weighed, in sufficient 0.1 *N* hydrochloric acid to make 100.0 ml.

Assay preparation—Weigh and powder not less than 20 Mepenzolate Bromide Tablets. Weigh accurately a portion of the powder equivalent to about 100 mg. of mepenzolate bromide, transfer to a 100-ml. volumetric flask, and add 60 ml. of 0.1 *N* hydrochloric acid. Shake for 30 minutes, dilute to volume with 0.1 *N* hydrochloric acid, mix, and filter through a dry paper, rejecting the first 10 ml. of filtrate.

Procedure—Transfer 5.0 ml. each of the *Assay preparation* and of the *Standard preparation* to separate separators. To each separator add 20 ml. of ammonium cobaltothiocyanate solution (prepared by dissolving 3.75 g. of cobaltous nitrate and 15.0 g. of ammonium thiocyanate in sufficient water to make 100 ml.), and shake for 1 minute. Extract with four 5-ml. portions of chloroform, collecting the extracts from each separator in a 25-ml. volumetric flask. Add chloroform to volume, and mix. If the solutions are turbid due to a suspension of water droplets, centrifuge to clarify. Concomitantly determine the absorbances of the clear solutions at 620 mμ, in 1-cm. cells, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the solution from the *Assay preparation* as A_U and that from the *Standard preparation* as A_S. Calculate the quantity, in mg., of $C_{21}H_{26}BrNO_3$, in the portion of the Tablets taken by the formula $100C \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of NF Mepenzolate Bromide Reference Standard in the *Standard preparation*.

Packaging and storage—Preserve Mepenzolate Bromide Tablets in well-closed containers.

Tablets available—Mepenzolate Bromide Tablets usually available contain the following amount of mepenzolate bromide: 25 mg.

CATEGORY and DOSE—See Mepenzolate Bromide.

Meperidine Hydrochloride Syrup

Meperidine Hydrochloride Syrup contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{15}H_{21}NO_2.HCl$.

Identification—Transfer 10 ml. of Meperidine Hydrochloride Syrup to a 125-ml. separator, add 40 ml. of water and 3 ml. of sodium hydroxide T.S., and extract with three 25-ml. portions of *n*-hexane. Wash the combined extracts with two 20-ml. portions of water, discard the water, and then extract with three 25-ml. portions of 0.1 *N* hydrochloric acid. Transfer the extracts to a 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix: the ultraviolet absorption spectrum of this solution exhibits maxima at about 251 mμ, 257 mμ, and 263 mμ, and minima at about 248 mμ, 254 mμ, and 260 mμ.

pH, page 824—The pH of Meperidine Hydrochloride Syrup is between 3.5 and 3.9.

Assay—Transfer to a separator an accurately measured volume of Meperidine Hydrochloride Syrup, equivalent to about 250 mg. of meperidine hydrochloride, and add 3 ml. of sodium hydroxide T.S. Extract with five 20-ml. portions of chloroform, and filter the extracts through a pledget of cotton into a 250-ml. conical flask. Wash the cotton with 5 ml. of chloroform, and add the washing to the combined filtrates. Add 10 ml. of glacial acetic acid and 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green endpoint. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 28.38 mg. of $C_{15}H_{21}NO_2.HCl$.

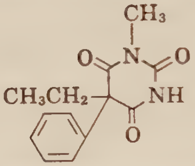
Packaging and storage—Preserve Meperidine Hydrochloride Syrup in tight, light-resistant containers.

Syrup available—Meperidine Hydrochloride Syrup usually available contains the following amount of meperidine hydrochloride: 50 mg. in 5 ml.

Category—Analgesic (narcotic).

Usual dose of meperidine hydrochloride—**50 mg.** every 4 hours.

Mephobarbital



5-Ethyl-1-methyl-5-phenylbarbituric Acid

$C_{13}H_{14}N_2O_3$ Mol. wt. 246.27

Mephobarbital, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{13}H_{14}N_2O_3$.

Description—Mephobarbital occurs as a white, crystalline powder. It is odorless and has a bitter taste. Its saturated solution is acid to litmus.

Solubility—Mephobarbital is slightly soluble in water, in alcohol, and in ether. It is soluble in chloroform, and in solutions of fixed alkali hydroxides and carbonates.

Identification—

A: Boil about 200 mg. of Mephobarbital with 10 ml. of sodium hydroxide T.S.: ammonia is evolved.

B: Shake about 60 mg. of Mephobarbital with 5 ml. of 0.05 *N* sodium hydroxide, and filter. To a 1-ml. portion of the filtrate add 3 drops of mercuric nitrate T.S.: a white precipitate, which is soluble in ammonia T.S., is formed. To another 1-ml. portion of the filtrate add silver nitrate T.S., dropwise: a white precipitate, which dissolves readily in ammonia T.S., is formed.

C: Add about 300 mg. of Mephobarbital to a mixture of 3 ml. of nitric acid and 2 ml. of sulfuric acid. Heat nearly to boiling, and maintain this temperature while shaking for 1 minute. Cool in ice, add about 15 ml. of water, and stir to promote precipitation. Cool again and filter. Wash the precipitate with 2 or 3 ml. of water, dry, and recrystallize from alcohol: the mononitromephobarbital so obtained melts between 155° and 160°, page 814.

Melting range, page 814—Mephobarbital melts between 176° and 181°.

Loss on drying, page 814—Dry Mephobarbital at 105° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Mephobarbital yields not more than 0.1 percent of residue on ignition.

Readily carbonizable substances, page 856—Dissolve 500 mg. of Mephobarbital in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid A.

Assay—Dissolve about 500 mg. of Mephobarbital, previously dried at 105° for 4 hours and accurately weighed, in 50 ml. of dimethylformamide in a 200-ml. flask. Add 4 drops of thymolphthalein T.S., and titrate with 0.1 *N* lithium methoxide, using a magnetic stirrer, and a cover for the flask to protect against atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* lithium methoxide is equivalent to 24.63 mg. of $C_{13}H_{14}N_2O_3$.

Packaging and storage—Preserve Mephobarbital in well-closed containers.

Category—Anticonvulsant; sedative.

Usual dose range—Anticonvulsant, **400** to **600 mg.** daily; sedative, **32** to **100 mg.** three or four times a day.

Mephobarbital Tablets

Mephobarbital Tablets contain not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{13}H_{14}N_2O_3$.

Identification—The mephobarbital obtained in the *Assay* of Mephobarbital Tablets melts between 174° and 181°, page 814, and responds to the *Identification tests* under *Mephobarbital*, page 410.

Disintegration, page 878—The disintegration time limit for Mephobarbital Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Mephobarbital Tablets meet the requirements of the content uniformity test for tablets.

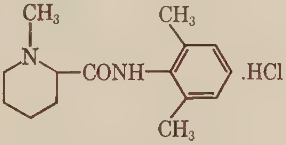
Assay—Weigh and finely powder not less than 20 Mephobarbital Tablets. Weigh accurately a portion of the powder, equivalent to about 300 mg. of mephobarbital, and transfer it to an extraction thimble. Extract the sample with 15 ml. of solvent hexane, allow the thimble to drain, transfer it to a continuous-extraction apparatus provided with a tared flask, and extract the mephobarbital with chloroform for 2 hours. Evaporate the chloroform on a steam bath with the aid of a current of air, cool, dissolve the residue in about 10 ml. of alcohol, re-evaporate, dry the residue at 105° for 1 hour, cool, and weigh. The weight of the residue represents the weight of $C_{13}H_{14}N_2O_3$ in the portion of the Tablets taken.

Packaging and storage—Preserve Mephobarbital Tablets in well-closed containers.

Tablets available—Mephobarbital Tablets usually available contain the following amounts of mephobarbital: 32, 50, 100, and 200 mg.

Category and Dose—See Mephobarbital.

Mepivacaine Hydrochloride*



(±)-1-Methyl-2′,6′-pipecoloxylidide Hydrochloride

$C_{15}H_{22}N_2O . HCl$ Mol. wt. 282.82

Mepivacaine Hydrochloride, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{15}H_{22}N_2O . HCl$.

Description—Mepivacaine Hydrochloride occurs as a white, odorless, crystalline solid. The pH of a 1 in 50 solution is about 4.5.

Solubility—Mepivacaine Hydrochloride is freely soluble in water and in methanol, very slightly soluble in chloroform, and practically insoluble in ether.

Identification—

A: A solution of Mepivacaine Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 808.

B: Dissolve about 250 mg. of Mepivacaine Hydrochloride in 10 ml. of water, add sufficient sodium carbonate T.S. to make slightly alkaline, extract the precipitate with ether, evaporate the ether extract to dryness on a steam bath, and dry the residue in vacuum at 60° for 1 hour: the mepivacaine so obtained melts between 149° and 153°, page 814.

Melting range, *Class Ia*, page 815—Mepivacaine Hydrochloride melts with decomposition between 255° and 262°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Mepivacaine Hydrochloride, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Mepivacaine Hydrochloride Reference Standard, similarly measured.

Loss on drying, page 814—Dry Mepivacaine Hydrochloride at 105° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Mepivacaine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 550 mg. of Mepivacaine Hydrochloride, previously dried at 105° for 4 hours and accurately weighed, to a 200-ml. tall form beaker, and dissolve it in 50 ml. of glacial acetic acid, heating if necessary. Add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 28.28 mg. of $C_{15}H_{22}N_2O . HCl$.

Packaging and storage—Preserve Mepivacaine Hydrochloride in well-closed containers.

Category—Local anesthetic.

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* Patented. See notice, page ii.

Mepivacaine Hydrochloride Injection

Mepivacaine Hydrochloride Injection is a sterile solution of mepivacaine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{15}H_{22}N_2O . HCl$.

Identification—

A: Mepivacaine Hydrochloride Injection responds to the tests for *Chloride,* page 808.

B: Extract a volume of Mepivacaine Hydrochloride Injection, equivalent to about 200 mg. of mepivacaine, with two 10-ml. portions of ether and discard the ether extracts. The remaining solution responds to *Identification test B* under *Mepivacaine Hydrochloride,* page 411.

pH, page 824—The pH of Mepivacaine Hydrochloride Injection is between 4.5 and 6.8.

Other requirements—Mepivacaine Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—Transfer to a 60-ml. separator an accurately measured volume of Mepivacaine Hydrochloride Injection, equivalent to about 40 mg. of mepivacaine hydrochloride. Dilute with water to 10 ml., add 1 ml. of sodium hydroxide T.S., and completely extract the mepivacaine with three 10-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water, filter the chloroform through a pledget of cotton, wash the filter with chloroform, add 2 drops of methyl red T.S. to the combined chloroform filtrate and washings, and titrate with 0.01 *N* perchloric acid in dioxane to a red end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* perchloric acid is equivalent to 2.828 mg. of $C_{15}H_{22}N_2O . HCl$.

Packaging and storage—Preserve Mepivacaine Hydrochloride Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injections available—Mepivacaine Hydrochloride Injection usually available contains the following amounts of mepivacaine hydrochloride: 3 percent in 1.8-ml. cartridges, 1 and 1.5 percent in 30 ml., 2 percent in 20 ml., 1 and 2 percent in 50 ml.

CATEGORY—See Mepivacaine Hydrochloride.

Mepivacaine Hydrochloride and Levonordefrin Injection

Mepivacaine Hydrochloride and Levonordefrin Injection is a sterile solution of mepivacaine hydrochloride and levonordefrin in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{15}H_{22}N_2O . HCl$ (mepivacaine hydrochloride) and not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (levonordefrin).

Identification—

A: Mepivacaine Hydrochloride and Levonordefrin Injection responds to the tests for *Chloride,* page 808.

B: Extract a volume of Mepivacaine Hydrochloride and Levonordefrin Injection, equivalent to about 200 mg. of mepivacaine, with two 10-ml. portions of ether and discard the ether extracts. The remaining solution responds to *Identification test B* under *Mepivacaine Hydrochloride,* page 411.

pH, page 824—The pH of Mepivacaine Hydrochloride and Levonordefrin Injection is between 3.3 and 5.5.

Other requirements—Mepivacaine Hydrochloride and Levonordefrin Injection meets the requirements under *Injections,* page 810.

Assay for mepivacaine hydrochloride—Transfer to a 60-ml. separator an accurately measured volume of Mepivacaine Hydrochloride and Levonordefrin Injection, equivalent to about 40 mg. of mepivacaine hydrochloride, and proceed as directed in the *Assay* under *Mepivacaine Hydrochloride Injection,* page 412, beginning with "Dilute with water to make 10 ml., and . . . ."

Assay for levonordefrin—Prepare a *Ferro-citrate solution, a Buffer solution,* and a *Standard preparation* as directed under *Epinephrine Assay,* page 803.

Assay preparation—Proceed as directed for *Assay preparation* under *Epinephrine Assay,* page 803, except change epinephrine to levonordefrin.

Procedure—Proceed as directed under *Epinephrine Assay,* page 803, except change epinephrine (base) to levonordefrin. When the *Ferro-citrate solution* and the *Buffer solution* are mixed with the

Assay preparation, a fine precipitate may form. This precipitate should be removed by centrifugation or by filtration through dry filter paper before the colorimetric measurements are taken.

Packaging and storage—Preserve Mepivacaine Hydrochloride and Levonordefrin Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Mepivacaine Hydrochloride and Levonordefrin Injection usually available contains the following amounts of mepivacaine hydrochloride and levonordefrin: 2 percent mepivacaine hydrochloride and 1 in 20,000 levonordefrin in 1.8-ml. cartridges and in 20-ml. multiple-dose vials.

CATEGORY—See Mepivacaine Hydrochloride.

Meprobamate Oral Suspension

Meprobamate Oral Suspension contains not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{18}N_2O_4$.

Identification—Mix 2 ml. of Meprobamate Oral Suspension with 2 ml. of acetone and 2 ml. of a solution of furfural in glacial acetic acid (1 in 100), add 5 ml. of hydrochloric acid, and shake: a purple color is produced which, on standing, changes to blue, then to blue-black, and finally to black-brown.

Assay—Transfer an accurately measured volume of Meprobamate Oral Suspension, equivalent to about 400 mg. of meprobamate, to a separator, and completely extract the meprobamate with 20-ml. portions of chloroform, filtering the extracts through a pledget of cotton enclosed in glass wool which has previously been moistened with chloroform. Collect the filtrate in a conical flask, add several glass beads to the flask, and evaporate to dryness on a steam bath. To the residue add 20 ml. of water, heat on a steam bath for several minutes, then add 40 ml. of hydrochloric acid, and reflux for 90 minutes. Remove the condenser, and continue boiling until the volume is reduced to about 20 ml. Cool to room temperature, add 50 ml. of water, and cool in an ice bath. Add 1 drop of methyl red T.S., and, while cooling continuously, cautiously neutralize with sodium hydroxide solution (4 in 10) until the indicator begins to change color. Add hydrochloric acid, if necessary, to restore the pink color, and then carefully neutralize with 0.1 *N* sodium hydroxide. Add 30 ml. of neutral formaldehyde solution (18 percent), and titrate with 0.1 *N* sodium hydroxide until the solution becomes yellow. Add 0.2 ml. of phenolphthalein T.S., and continue the titration with 0.1 *N* sodium hydroxide to a distinct pink color. Perform a blank determination, and make any necessary correction. Each ml. of the total volume of 0.1 *N* sodium hydroxide consumed after the addition of the formaldehyde solution is equivalent to 10.91 mg. of $C_9H_{18}N_2O_4$.

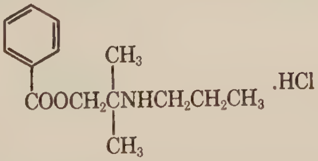
Packaging and storage—Preserve Meprobamate Oral Suspension in tight containers.

Suspension available—Meprobamate Oral Suspension usually available contains the following amount of meprobamate: 200 mg. in 5 ml.

CATEGORY—Tranquilizer (minor).

USUAL DOSE OF MEPROBAMATE—**400 mg.** three or four times a day.

Meprylcaine Hydrochloride*



2-Methyl-2-(propylamino)-1-propanol Benzoate (Ester) Hydrochloride

$C_{14}H_{21}NO_2 . HCl$ Mol. wt. 271.79

Meprylcaine Hydrochloride, dried in a vacuum desiccator over phosphorus pentoxide for 6 hours, contains not less than 98.5 percent and not more than 101.5 percent of $C_{14}H_{21}NO_2 . HCl$.

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* Patented. See notice, page ii.

Description—Meprylcaine Hydrochloride occurs as a white, odorless, crystalline solid. The pH of a 1 in 50 solution is about 5.7.

Solubility—Meprylcaine Hydrochloride is freely soluble in water, in alcohol, and in chloroform. It is slightly soluble in acetone.

Identification—

A: A solution of Meprylcaine Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 808.

B: Dissolve about 100 mg. of Meprylcaine Hydrochloride in 10 ml. of water, heat almost to boiling, and add, with stirring, 1 ml. of a saturated solution of picric acid in 20 percent alcohol. Cool slowly, collect the precipitate on a filter, wash with a few small portions of water, and dry in a vacuum desiccator over phosphorus pentoxide for 18 hours: the picrate so obtained melts with decomposition between 196° and 200°, page 814. (*Caution: Picrates may be explosive.*)

C: Dissolve about 100 mg. of Meprylcaine Hydrochloride in 10 ml. of diluted hydrochloric acid, cool to 0° in an ice bath, and introduce 5 ml. of a solution of sodium nitrite (1 in 5), stirring gently. Add 2 ml. of a solution of 100 mg. of beta-naphthol in 5 ml. of sodium hydroxide T.S. and observe immediately: the solution turns green in color, and no bright orange-red precipitate is formed (*absence of a primary aminophenyl group*).

Melting range, page 814—Meprylcaine Hydrochloride melts between 150° and 152°.

Loss on drying, page 814—Dry Meprylcaine Hydrochloride in a vacuum desiccator over phosphorus pentoxide for 6 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Meprylcaine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 150 mg. of Meprylcaine Hydrochloride, previously dried in a vacuum desiccator over phosphorus pentoxide for 6 hours and accurately weighed, to a separator, dissolve the sample in 20 ml. of water, add 3 ml. of ammonia T.S., and completely extract the meprylcaine with 20-ml. portions of isooctane. Filter the isooctane extracts into a beaker, wash the filter with isooctane, and evaporate the combined filtrate and washings in a current of warm air nearly to dryness. To the residue add 5 ml. of neutralized alcohol and 40.0 ml. of 0.02 *N* sulfuric acid, and heat on a steam bath until the odor of isooctane is no longer perceptible. Cool, add 2 drops of methyl red T.S., and titrate with 0.02 *N* sodium hydroxide (see *Residual Titrations*, page 883). Each ml. of 0.02 *N* sulfuric acid is equivalent to 5.436 mg. of $C_{14}H_{21}NO_2 . HCl$.

Packaging and storage—Preserve Meprylcaine Hydrochloride in well-closed containers.

CATEGORY—Local anesthetic.

Meprylcaine Hydrochloride and Epinephrine Injection

Meprylcaine Hydrochloride and Epinephrine Injection is a sterile solution of meprylcaine hydrochloride and epinephrine in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_{21}NO_2 . HCl$ (meprylcaine hydrochloride) and not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (epinephrine).

Identification—Meprylcaine Hydrochloride and Epinephrine Injection responds to *Identification tests B* and *C* under *Meprylcaine Hydrochloride*, page 413.

Other requirements—Meprylcaine Hydrochloride and Epinephrine Injection meets the requirements under *Injections*, page 810.

Assay for meprylcaine hydrochloride—Transfer to a separator an accurately measured volume of Meprylcaine Hydrochloride and Epinephrine Injection, equivalent to about 150 mg. of meprylcaine hydrochloride, and proceed as directed in the *Assay* under *Meprylcaine Hydrochloride*, page 413, beginning with "... add 3 ml. of ammonia T.S. ..."

Assay for epinephrine—Prepare a *Ferro-citrate solution*, *a Buffer solution*, and a *Standard preparation* as directed under *Epinephrine Assay*, page 803.

Assay preparation—Proceed as directed for *Assay preparation* under *Epinephrine Assay*, page 803.

Procedure—Proceed as directed for *Procedure* under *Epinephrine Assay*, page 803.

Packaging and storage—Preserve Meprylcaine Hydrochloride and Epinephrine Injection in single-dose containers, preferably of Type I glass.

Injections available—Meprylcaine Hydrochloride and Epinephrine Injection usually available contains the following amounts of meprylcaine hydrochloride and epinephrine: 2 percent meprylcaine hydrochloride and 1 in 50,000 epinephrine in 2-ml. and 2.5-ml. cartridges and in 20-ml. bottles.

CATEGORY—See Meprylcaine Hydrochloride.

Yellow Mercuric Oxide

HgO Mol. wt. 216.59

Yellow Mercuric Oxide, dried at 105° for 2 hours, contains not less than 99.5 percent and not more than 100.5 percent of HgO.

Description—Yellow Mercuric Oxide occurs as a yellow to orange-yellow, heavy, impalpable powder. It is odorless, and is stable in air, but becomes discolored on exposure to light. It is not alkaline when moistened with hot water.

Solubility—Yellow Mercuric Oxide is practically insoluble in water, and is insoluble in alcohol. It is readily soluble in diluted hydrochloric or diluted nitric acid, forming colorless solutions.

Identification—Mix 1 g. of Yellow Mercuric Oxide with 20 ml. of water, and add just enough hydrochloric acid, dropwise, to effect solution: this solution responds to the tests for *Mercuric Salts*, page 809.

Loss on drying, page 814—Dry Yellow Mercuric Oxide at 105° for 2 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Yellow Mercuric Oxide yields not more than 0.2 percent of residue on ignition.

Acid-insoluble substances—A solution of 500 mg. of Yellow Mercuric Oxide in 25 ml. of either diluted hydrochloric acid or diluted nitric acid is not more than slightly turbid.

Distinction from red mercuric oxide—Dissolve 1 g. of oxalic acid in 1 ml. of ammonia T.S., diluted with 10 ml. of water. To this solution add 500 mg. of Yellow Mercuric Oxide, and heat the mixture in a test tube on a steam bath for 2 hours, replacing from time to time the water lost by evaporation: the Oxide is converted into white or yellowish white mercuric oxalate.

Assay—Dry about 300 mg. of Yellow Mercuric Oxide at 105° for 2 hours, weigh accurately, dissolve it in a mixture of 10 ml. of water and 5 ml. of nitric acid, and dilute the solution with 150 ml. of cold water. Then add 2 ml. of ferric ammonium sulfate T.S., and titrate with 0.1 N ammonium thiocyanate. Each ml. of 0.1 N ammonium thiocyanate is equivalent to 10.83 mg. of HgO.

Packaging and storage—Preserve Yellow Mercuric Oxide in well-closed, light-resistant containers.

CATEGORY—Local anti-infective (ophthalmic).

APPLICATION—To the conjunctiva as a 1 percent ointment.

Yellow Mercuric Oxide Ophthalmic Ointment

Caution: During its manufacture and storage, Yellow Mercuric Oxide Ophthalmic Ointment must not come into contact with metallic utensils or containers except those made of stainless steel, tin, or tin-coated material.

Yellow Mercuric Oxide Ophthalmic Ointment contains not less than 0.9 percent and not more than 1.1 percent of HgO.

Yellow Mercuric Oxide, in very fine powder	**10 g.**
Mineral Oil	**10 g.**
White Ointment	**980 g.**
To make	**1000 g.**

Levigate the yellow mercuric oxide with the mineral oil until the mixture is smooth, and then incorporate the white ointment (see page 8).

Weight variation, page 901—Yellow Mercuric Oxide Ophthalmic Ointment meets the requirements of the weight variation test for ointments.

Metal particles—Yellow Mercuric Oxide Ophthalmic Ointment meets the requirements of the test for *Metal Particles—Ophthalmic Ointments*, page 816.

Assay—Transfer an accurately weighed quantity of Yellow Mercuric Oxide Ophthalmic Ointment, equivalent to about 100 mg. of yellow mercuric oxide, to a stoppered flask with the aid of 20 ml. of chloroform. Add 10 ml. of diluted nitric acid and 20 ml. of water, and shake until the mercuric oxide is dissolved. Add 50 ml. of water and 2 ml. of ferric ammonium sulfate T.S., and titrate with 0.1 *N* ammonium thiocyanate at a temperature not exceeding 20°. Each ml. of 0.1 *N* ammonium thiocyanate is equivalent to 10.83 mg. of HgO.

Packaging and storage—Preserve Yellow Mercuric Oxide Ophthalmic Ointment in collapsible ophthalmic tubes.

Category—See Yellow Mercuric Oxide.

Mestranol Tablets

Mestranol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{26}O_2$.

Identification—The absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits a maximum at 545 ± 3 mμ.

Disintegration, page 878—The disintegration time limit for Mestranol Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Mestranol Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure.

Color reagent—Prepare as directed in the *Assay.*

Standard preparation—Transfer about 8 mg. of USP Mestranol Reference Standard, accurately weighed, to a 200-ml. volumetric flask, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Test preparation—Transfer one tablet to a 60-ml. separator containing 5.0 ml. of water and 0.05 ml. of sodium hydroxide solution (1 in 2). Carefully add 20.0 ml. of chloroform, stopper the separator with a stopper moistened with water, and shake until the tablet has completely disintegrated. Shake 3 minutes longer to ensure complete solution of the mestranol. Separate and drain most of the chloroform layer into a 25-ml. glass-stoppered flask containing about 3 g. of anhydrous sodium sulfate, stopper, and mix well. Use the chloroform solution as directed in the *Procedure.*

Procedure—Transfer 4.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 25-ml. volumetric flasks, wash down the neck of each flask with 2 ml. of chloroform, and then evaporate each to dryness with the aid of a slow current of air, without heating. To each flask add 0.3 ml. of methanol, then stopper the flasks and rotate to dissolve the residue completely. Immerse the bulb and part of the neck of each flask in a water bath maintained at 25°, and, with constant swirling, add 10.0 ml. of the *Color reagent* to each flask. Remove the flasks from the water bath, stopper, and mix thoroughly by swirling and inversion. (*Caution:* Do not shake.) Six minutes after the addition of the *Color reagent,* concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 545 mμ, with a suitable spectrophotometer, using the *Color reagent* as the blank. Calculate the quantity, in mcg., of $C_{21}H_{26}O_2$ in the Tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mcg., of mestranol in the tablet; D is the exact concentration, in mcg. per ml., of mestranol in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the *Standard preparation;* A_U is the absorbance of the final sample solution; and A_S is the absorbance of the solution from the *Standard preparation.*

Assay—

Color reagent—Transfer 30.0 ml. of methanol to a 100-ml. volumetric flask, and place the flask in an ice water bath. Keeping the temperature below 15°, and with constant stirring, slowly and cautiously add sulfuric acid until a volume of about 95 ml. is reached. Allow the solution to return to room temperature, dilute to volume with sulfuric acid, and mix.

Standard preparation—Transfer about 16 mg. of USP Mestranol Reference Standard, accurately weighed, to a 200-ml. volumetric flask, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparation—Transfer a number of Mestranol Tablets, equivalent to about 1.6 mg. of mestranol, to a 125-ml. separator containing 30 ml. of water, 0.15 ml. of sodium hydroxide solution (1 in 2), and 40 ml. of chloroform. Stopper the separator, and shake until disintegration is complete. Separate and drain the chloroform layer, through a filter funnel containing 10 g. of anhydrous sodium sulfate, into a 200-ml. volumetric flask. Extract with three additional 40-ml. portions of chloroform, passing each in succession through the filter and into the flask.

Rinse the filter with chloroform into the flask, dilute to volume with chloroform, and mix.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 25-ml. volumetric flasks, wash down the neck of each flask with 2 ml. of chloroform, and then evaporate each to dryness with the aid of a slow current of air, without heating. To each flask add 0.3 ml. of methanol, then rotate the flasks to dissolve the residues completely. Submerge the flasks in a water bath maintained at 25°, and, with constant swirling, add 10.0 ml. of the *Color reagent* to each flask. Remove the flasks from the water bath, stopper, and mix thoroughly by swirling and inversion. (*Caution:* Do not shake.) Six minutes after the addition of the *Color reagent*, concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 545 mμ, with a suitable spectrophotometer, using the *Color reagent* as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{26}O_2$ in the Tablets taken by the formula $0.2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Mestranol Tablets in well-closed containers.

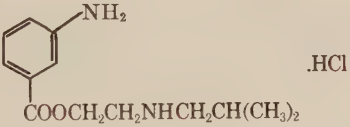
Tablets available—Mestranol Tablets usually available contain the following amounts of mestranol: 80 and 100 mcg.

Category—Estrogen.

Usual dose of mestranol—**80** to **100 mcg.** daily for 20 days of each menstrual cycle.

Mestranol and Chlormadinone Acetate Tablets, page 152

Metabutethamine Hydrochloride



2-(Isobutylamino)ethanol *m*-Aminobenzoate (Ester) Monohydrochloride

$C_{13}H_{20}N_2O_2 . HCl$ Mol. wt. 272.78

Metabutethamine Hydrochloride, dried in a vacuum desiccator over phosphorus pentoxide for 6 hours, contains not less than 98.5 percent and not more than 100.5 percent of $C_{13}H_{20}N_2O_2 . HCl$.

Description—Metabutethamine Hydrochloride occurs as a white, odorless, crystalline solid. The pH of a 1 in 50 solution is about 6.

Solubility—Metabutethamine Hydrochloride is soluble in water. It is slightly soluble in alcohol, in acetone, and in chloroform.

Identification—

A: A solution of Metabutethamine Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 808.

B: Dissolve about 100 mg. of Metabutethamine Hydrochloride in 10 ml. of water, heat almost to boiling, and add, with stirring, 1 ml. of a saturated solution of picric acid in 20 percent alcohol. Cool slowly, collect the precipitate on a filter, wash with a few small portions of water, and dry in a vacuum desiccator over phosphorus pentoxide for 18 hours: the picrate so obtained melts between 147° and 149°, page 814. (*Caution: Picrates may be explosive.*)

C: Dissolve about 100 mg. of Metabutethamine Hydrochloride in 5 ml. of water. Add 0.5 ml. of this solution to a solution prepared immediately before use by mixing 0.5 to 1 ml. of stronger ammonia water with 1 ml. of a reagent consisting of 500 mg. of nickel chloride hexahydrate in 100 ml. of water with sufficient carbon disulfide to be in excess of saturation: a deep green color is formed immediately, followed in a few minutes by the formation of a green precipitate (*presence of a secondary amino group*).

Melting range, page 814—Metabutethamine Hydrochloride melts between 181° and 184°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Metabutethamine Hydrochloride, previously dried in a vacuum desiccator over phosphorus pentoxide for 6 hours, exhibits maxima only at the same wavelengths as that of NF Metabutethamine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 886—The

ultraviolet absorption spectrum of a 1 in 50,000 solution of Metabutethamine Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Metabutethamine Hydrochloride Reference Standard, similarly measured.

Loss on drying, page 814—Dry Metabutethamine Hydrochloride in a vacuum desiccator over phosphorus pentoxide for 6 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Metabutethamine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 200 mg. of Metabutethamine Hydrochloride, previously dried in a vacuum desiccator over phosphorus pentoxide for 6 hours and accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a 1000-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Metabutethamine Hydrochloride Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 315 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2.HCl$ in the Metabutethamine Hydrochloride taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Metabutethamine Hydrochloride in well-closed containers.

CATEGORY—Local anesthetic (dental).

Metabutethamine Hydrochloride and Epinephrine Injection

Metabutethamine Hydrochloride and Epinephrine Injection is a sterile solution of metabutethamine hydrochloride and epinephrine in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O_2.HCl$ (metabutethamine hydrochloride), and not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (epinephrine).

Identification—Metabutethamine Hydrochloride and Epinephrine Injection responds to *Identification tests B* and *C* under *Metabutethamine Hydrochloride*, page 417.

Other requirements—Metabutethamine Hydrochloride and Epinephrine Injection meets the requirements under *Injections*, page 810.

Assay for metabutethamine hydrochloride—Transfer to a separator an accurately measured volume of Metabutethamine Hydrochloride and Epinephrine Injection, equivalent to about 150 mg. of metabutethamine hydrochloride, add 3 ml. of ammonia T.S., and completely extract the metabutethamine with 20-ml. portions of chloroform. Filter the chloroform extracts and wash the filter with chloroform, then evaporate the combined filtrates and washings in a current of warm air to dryness. Dry the residue at 60° for 2 hours, and weigh. Each mg. of the residue is equivalent to 1.154 mg. of $C_{13}H_{20}N_2O_2.HCl$.

Assay for epinephrine—Prepare a *Ferro-citrate solution, a Buffer solution,* and a *Standard preparation* as directed under *Epinephrine Assay*, page 803.

Assay preparation—Proceed as directed for *Assay preparation* under *Epinephrine Assay*, page 803.

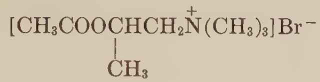
Procedure—Proceed as directed for *Procedure* under *Epinephrine Assay*, page 803.

Packaging and storage—Preserve Metabutethamine Hydrochloride and Epinephrine Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Metabutethamine Hydrochloride and Epinephrine Injection usually available contains the following amounts of metabutethamine hydrochloride and epinephrine: 3.8 percent metabutethamine hydrochloride and 1 in 60,000 epinephrine in 2-ml. cartridges and in 30-ml. bottles.

CATEGORY—See Metabutethamine Hydrochloride.

Methacholine Bromide



$$[CH_3COO\underset{\substack{| \\ CH_3}}{CH}CH_2\overset{+}{N}(CH_3)_3]Br^-$$

(2-Hydroxypropyl)trimethylammonium Bromide Acetate

$C_8H_{18}BrNO_2$ Mol. wt. 240.14

Methacholine Bromide, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_8H_{18}BrNO_2$.

Description—Methacholine Bromide occurs as a white, crystalline powder, possessing a slight amine-like odor. It is very hygroscopic. The pH of a freshly prepared 1 in 20 solution of Methacholine Bromide is about 5.

Solubility—Methacholine Bromide is freely soluble in water and in alcohol. It is practically insoluble in benzene and in ether.

Identification—

A: Dissolve about 1 g. of Methacholine Bromide in 10 ml. of water. To a 1-ml. portion add 1 ml. of alcohol and 1 ml. of sulfuric acid and heat on a steam bath: the odor of ethyl acetate is perceptible (*presence of an acetyl group*). To a 5-ml. portion add 2.5 g. of potassium hydroxide and heat: the odor of trimethylamine is perceptible (*presence of an amine*). To the remaining portion add an excess of silver nitrate T.S.: a light yellow, curdy precipitate forms which is only slightly soluble in ammonia T.S. (*presence of bromide*).

B: Dissolve 200 mg. of Methacholine Bromide in 2 ml. of sulfuric acid: a brown hygroscopic gas is evolved immediately, and the solution turns orange-brown (*presence of bromine; distinction from methacholine chloride*).

C: To a few crystals of Methacholine Bromide on a microscope slide add several drops of platinic chloride T.S.: small rhombohedric plates form (*distinction from acetylcholine chloride, which forms needles, and choline chloride, which forms no crystals*).

Melting range, page 814—Methacholine Bromide melts between 147° and 150°.

Loss on drying, page 814—Dry Methacholine Bromide at 105° for 4 hours: it loses not more than 1.5 percent of its weight.

Residue on ignition, page 858—Methacholine Bromide yields not more than 0.1 percent of residue on ignition.

Acetylcholine—To 2 ml. of a solution of Methacholine Bromide (1 in 10) add 3 ml. of a solution of sodium perchlorate (1 in 5), shake well, and cool in ice water: no precipitate forms.

Assay—Transfer to a conical flask about 500 mg. of Methacholine Bromide, previously dried at 105° for 4 hours and accurately weighed (because it is very hygroscopic, store the dried material in a vacuum desiccator), dissolve it in 50 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 24.01 mg. of $C_8H_{18}BrNO_2$.

Packaging and storage—Preserve Methacholine Bromide in tight containers.

CATEGORY—Cholinergic.

USUAL DOSE—**200 mg.** two or three times a day.

USUAL DOSE RANGE—**200** to **600 mg.**

Methacholine Bromide Tablets

Methacholine Bromide Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_{18}BrNO_2$.

Identification—Transfer to a glass-stoppered, 50-ml. conical flask an amount of powdered Methacholine Bromide Tablets, equivalent to about 1.5 g. of methacholine bromide, add 15 ml. of water, and shake mechanically for 15 minutes. Filter, pass water through the filter to make a total of 15 ml. of filtrate, and mix. The filtrate responds to *Identification tests A* and *B* under *Methacholine Bromide,* page 419.

Disintegration, page 878—The disintegration time limit for Methacholine Bromide Tablets is 30 minutes.

Weight variation, page 901—Methacholine Bromide Tablets meet the requirements of the weight variation test for tablets.

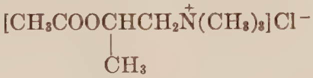
Assay—Weigh and finely powder not less than 20 Methacholine Bromide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 300 mg. of methacholine bromide, to a beaker, add 25 ml. of methanol, and heat to boiling on a steam bath. Decant the warm methanol through a sintered-glass funnel, collecting the filtrate in a 250-ml. beaker, and repeat the extraction with five 20-ml. portions of methanol. Evaporate the methanol solution just to dryness on a steam bath, dissolve the residue in 50 ml. of glacial acetic acid with the aid of heat, and allow to cool. Add 10 ml. of mercuric acetate T.S., and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 24.01 mg. of $C_8H_{18}BrNO_2$.

Packaging and storage—Preserve Methacholine Bromide Tablets in tight containers.

Tablets available—Methacholine Bromide Tablets usually available contain the following amount of methacholine bromide: 200 mg.

Category and Dose—See Methacholine Bromide.

Methacholine Chloride



$$[CH_3COO\underset{CH_3}{\underset{|}{CH}}CH_2\overset{+}{N}(CH_3)_3]Cl^-$$

(2-Hydroxypropyl)trimethylammonium Chloride Acetate

$C_8H_{18}ClNO_2$ Mol. wt. 195.69

Methacholine Chloride, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_8H_{18}ClNO_2$.

Description—Methacholine Chloride occurs as colorless or white crystals, or as a white, crystalline powder. It is odorless or has a slight odor, and is very hygroscopic. Its solutions are neutral to litmus.

Solubility—Methacholine Chloride is very soluble in water, and is freely soluble in alcohol and in chloroform.

Identification—

A: To about 100 mg. of Methacholine Chloride on a watch glass add 3 ml. of platinic chloride T.S. previously diluted with 2 ml. of water: small rhombohedric plates are formed, which melt between 220° and 225°, page 814 (*distinction from acetylcholine chloride, which forms needles radiating from a central point, and from choline chloride, which forms no crystals*).

B: To 1 ml. of a solution of Methacholine Chloride (1 in 10) add 1 ml. of alcohol and 1 ml. of sulfuric acid, and heat gently: the odor of ethyl acetate becomes perceptible.

C: To 5 ml. of a solution of Methacholine Chloride (1 in 10) add 2 g. of potassium hydroxide and heat gently: the odor of trimethylamine is perceptible.

D: A solution of Methacholine Chloride (1 in 50) responds to the tests for *Chloride*, page 808.

Melting range, page 814—Dissolve about 100 mg. of Methacholine Chloride in 2 to 3 ml. of chloroform in a small beaker. Heat at 110° for 1 hour. Quickly powder the dry residue, while still hot, with a glass rod and transfer to a melting point tube in the usual manner. Determine the melting range without delay. Methacholine Chloride melts between 170° and 173°.

Loss on drying, page 814—Dry Methacholine Chloride at 105° for 4 hours: it loses not more than 1.5 percent of its weight.

Residue on ignition, page 858—Methacholine Chloride yields not more than 0.1 percent of residue on ignition.

Acetylcholine chloride—To 2 ml. of Methacholine Chloride solution (1 in 10) add 3 ml. of a solution of sodium perchlorate (1 in 5), shake well, and immerse in ice water for 5 minutes: no precipitate is formed.

Assay—Transfer to a conical flask about 400 mg. of Methacholine Chloride, previously dried at 105° for 4 hours and accurately weighed (because it is very hygroscopic, store the dried material in a vacuum desiccator), dissolve it in 50 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 19.57 mg. of $C_8H_{18}ClNO_2$.

Packaging and storage—Preserve Methacholine Chloride in tight containers.

Category—Cholinergic.

Usual dose—Subcutaneous, initial, **10 mg.**; then may give **25 mg.** 10 to 30 minutes later.

Usual dose range—**10 to 40 mg.**

Sterile Methacholine Chloride

Sterile Methacholine Chloride, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_8H_{18}ClNO_2$.

Description and other requirements—Sterile Methacholine Chloride conforms to the *Description* and meets the *Identification tests* and the other requirements under *Methacholine Chloride,* page 420.

Completeness of solution—Place 1 g. of Sterile Methacholine Chloride in a 10-ml. glass-stoppered cylinder, nearly fill to the 10-ml. mark with water, and shake gently until dissolved: the solution is clear.

Sterility—Sterile Methacholine Chloride meets the requirements under *Sterility Tests,* page 874.

Weight variation, page 901—Sterile Methacholine Chloride meets the requirements of the weight variation test for sterile solids, and the mean net weight so determined is not less than 90 percent and not more than 110 percent of the labeled amount.

Assay—Proceed as directed in the *Assay* under *Methacholine Chloride,* page 420.

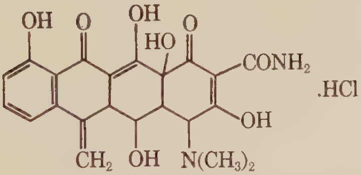
Packaging and storage—Preserve Sterile Methacholine Chloride in hermetic or other suitable containers so closed that the sterility of the product is maintained until the package is opened for use.

Labeling—Sterile Methacholine Chloride complies with the requirements for *Labeling* under *Injections,* page 810.

Size available—Sterile Methacholine Chloride is usually available in the following amount: 25 mg.

CATEGORY and DOSE—See Methacholine Chloride.

Methacycline Hydrochloride*



4-(Dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,5,10,12,12*a*-pentahydroxy-6-methylene-1,11-dioxo-2-naphthacenecarboxamide Monohydrochloride

$C_{22}H_{22}N_2O_8 . HCl$ Mol. wt. 478.89

Methacycline Hydrochloride has a potency of not less than 832 mcg. of $C_{22}H_{22}N_2O_8$ (methacycline) per mg. Methacycline Hydrochloride conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Methacycline Hydrochloride occurs as a yellow to dark yellow crystalline powder. The pH of a 1 percent solution is between 2 and 3.

Solubility—Methacycline Hydrochloride is freely soluble in water.

Packaging and storage—Preserve Methacycline Hydrochloride in tight, light-resistant containers in a cool place.

CATEGORY—Antibacterial.

USUAL DOSE—**600 mg.** (equivalent to 560 mg. of methacycline base) daily in divided doses.

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* Patented. See notice, page ii.

Methacycline Hydrochloride Capsules

Methacycline Hydrochloride Capsules contain methacycline hydrochloride equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{22}H_{22}N_2O_8$ (methacycline base). Methacycline Hydrochloride Capsules conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Methacycline Hydrochloride Capsules in tight, light-resistant containers.

Capsules available—Methacycline Hydrochloride Capsules usually available contain the following amounts of methacycline hydrochloride: 150 mg. (equivalent to 140 mg. of methacycline) and 300 mg. (equivalent to 280 mg. of methacycline).

CATEGORY and DOSE—See Methacycline Hydrochloride.

Methacycline Hydrochloride Oral Suspension

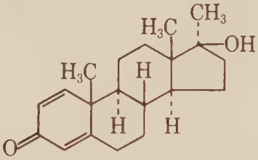
Methacycline Hydrochloride Oral Suspension contains methacycline hydrochloride and one or more suitable and harmless buffers, dispersants, diluents, colorings, flavorings, and preservatives. It contains not less than 90.0 percent and not more than 125.0 percent of the labeled amount of $C_{22}H_{22}N_2O_8$ (methacycline base). Methacycline Hydrochloride Oral Suspension conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Methacycline Hydrochloride Oral Suspension in tight, light-resistant containers in a cool place.

Suspension available—Methacycline Hydrochloride Oral Suspension usually available contains the following amount of methacycline hydrochloride: 75 mg. (equivalent to 70 mg. of methacycline) in 5 ml.

CATEGORY and DOSE—See Methacycline Hydrochloride.

Methandrostenolone*



17β-Hydroxy-17-methylandrosta-1,4-dien-3-one

$C_{20}H_{28}O_2$ Mol. wt. 300.44

Methandrostenolone contains not less than 97.0 percent and not more than 103.0 percent of $C_{20}H_{28}O_2$, calculated on the dried basis.

Description—Methandrostenolone occurs as white crystals or as a white crystalline powder. It is odorless.

Solubility—Methandrostenolone is insoluble in water. It is soluble in alcohol, in chloroform, and in glacial acetic acid, and is slightly soluble in ether.

Identification—Prepare a solution of Methandrostenolone in chloroform containing 2 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution and 10 μl. of a chloroform solution of NF Methandrostenolone Reference Standard containing 2 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and methanol (96:4) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methandrostenolone, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Methandrostenolone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The

ultraviolet absorption spectrum of a 1 in 100,000 solution of Methandrostenolone in methanol exhibits maxima and minima at the same wavelengths as that of NF Methandrostenolone Reference Standard, similarly measured.

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* Patented. See notice, page ii.

Melting range, page 814—Methandrostenolone melts with decomposition between 160° and 166°.

Specific rotation, page 822—The specific rotation of Methandrostenolone, calculated on the dried basis, determined in a solution in alcohol containing 200 mg. of Methandrostenolone in each 10 ml., is between +9° and +17°.

Loss on drying, page 814—Dry Methandrostenolone at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Methandrostenolone yields not more than 0.2 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 200 mg. of Methandrostenolone meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Methyltestosterone—Prepare a solution of Methandrostenolone in chloroform containing 2 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution, 10 μl. of a chloroform solution of NF Methandrostenolone Reference Standard containing 2 mg. per ml., and 10 μl. of a chloroform solution of NF Methyltestosterone Reference Standard containing 10 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and methanol (96:4) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with a formaldehyde solution (prepared by cautiously dissolving 0.8 ml. of formaldehyde in 10 ml. of sulfuric acid and then adding 3 ml. of water), followed by heating on a hot plate for 5 to 10 minutes, and inspecting under ambient lighting and longwave ultraviolet light: no more than three spots, in addition to that produced by methandrostenolone, are found, and any spot occurring at the same R_f as methyltestosterone is not greater in size or intensity than that produced by NF Methyltestosterone Reference Standard (0.5 percent as methyltestosterone).

Assay—Transfer about 50 mg. of Methandrostenolone, accurately weighed, to a 250-ml. volumetric flask, add methanol to volume, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methandrostenolone Reference Standard, in methanol, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 245 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{20}H_{28}O_2$ in the Methandrostenolone taken, by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Methandrostenolone in tight, light-resistant containers.

CATEGORY—Androgen.
USUAL DOSE—**2.5** to **5 mg.** daily.

Methandrostenolone Tablets

Methandrostenolone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{28}O_2$.

Identification—

A: Triturate a quantity of finely powdered Methandrostenolone Tablets, equivalent to about 10 mg. of methandrostenolone, with 5 ml. of chloroform, and filter. Proceed as directed for *Identification* under *Methandrostenolone,* page 422, beginning with "On a suitable thin-layer chromatographic plate . . . ."

B: The ultraviolet absorption spectrum of the solution employed for measurement of the absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of the solution of NF Methandrostenolone Reference Standard, similarly measured.

Dissolution, *Method I,* page 802—Not less than 50 percent of the labeled amount of $C_{20}H_{28}O_2$ in Methandrostenolone Tablets dissolves into solution within 45 minutes, using a stirring speed of 100 r.p.m. and water as the *Dissolution Fluid.* Determine the amount of $C_{20}H_{28}O_2$ in solution by determining the ultraviolet absorption of aliquots removed from the dissolution solution, at 245 mμ, in 1-cm. cells, with a suitable spectrophotometer, using water as the blank and utilizing a standard curve, representing absorbance *versus* concentration of NF Methandrostenolone Reference Standard.

Content uniformity, *Method II,* page 799—Place a Methandrostenolone Tablet in a 100-ml. volumetric flask, and gently pulverize with a glass rod. Add 3 ml. of water, mix well, and then add 50 ml. of methanol. Shake mechanically for 5 minutes, dilute to volume with methanol, and mix. Centrifuge a portion of the solution, and dilute a portion of the supernatant liquid, quantitatively and stepwise, if necessary, with methanol to provide a solution containing approximately 10 mcg. of methandrostenolone per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Methandrostenolone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 245 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{20}H_{28}O_2$ in the Tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of methandrostenolone, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of methandrostenolone in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

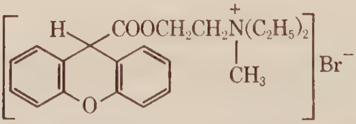
Assay—Weigh and finely powder not less than 20 Methandrostenolone Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg. of methandrostenolone, to a separator, add 25 ml. of water, and mix well. Extract the methandrostenolone completely, using three 25-ml. portions of chloroform, filtering each portion through chloroform-washed cotton into a 100-ml. volumetric flask. Dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this solution to a 50-ml. volumetric flask, and evaporate on a steam bath with the aid of a current of air just to dryness. Dissolve the residue in methanol, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methandrostenolone Reference Standard, in methanol, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 245 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{20}H_{28}O_2$ in the portion of the Tablets taken, by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Methandrostenolone Tablets in tight, light-resistant containers.

Tablets available—Methandrostenolone Tablets usually available contain the following amounts of methandrostenolone: 2.5 and 5.0 mg.

CATEGORY and DOSE—See Methandrostenolone.

Methantheline Bromide*



Diethyl(2-hydroxyethyl)methylammonium Bromide Xanthene-9-carboxylate

$C_{21}H_{26}BrNO_3$ Mol. wt. 420.35

Methantheline Bromide contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{26}BrNO_3$, calculated on the dried basis.

Description—Methantheline Bromide is a white or nearly white powder. It has a very bitter taste, and is practically odorless. Its solutions have a pH of about 5.

Solubility—Methantheline Bromide is very soluble in water, is freely soluble in alcohol and in chloroform, and is practically insoluble in ether. Its water solution decomposes on standing.

Identification—

A: Dissolve about 250 mg. of Methantheline Bromide in 10 ml. of water. To 2 ml. of the solution, add 5 ml. of water, 2 ml. of diluted nitric acid, and 2 ml. of silver nitrate T.S.: a light yellow, curdy precipitate forms which is only slightly soluble in ammonia T.S. To the remainder of the solution add 10 ml. of sodium hydroxide T.S., and heat to boiling. Keep the mixture hot for about 2 minutes, cool slightly, and acidify with about 5 ml. of diluted hydrochloric acid. Cool, filter, wash the precipitate thoroughly with water, recrystallize from 50 percent alcohol, and dry at 105° for 1 hour: the xanthanoic acid so obtained melts between 218° and 223°, page 814.

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* Patented. See notice, page ii.

B: Place about 10 mg. of the crystals obtained in *Identification test A* in a test tube, and add 5 ml. of sulfuric acid: a bright yellow to orange solution is obtained.

Melting range, page 814—Methantheline Bromide melts between 171° and 177°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methantheline Bromide, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Methantheline Bromide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Methantheline Bromide in methanol exhibits maxima and minima at the same wavelengths as that of NF Methantheline Bromide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 282 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Methantheline Bromide at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Methantheline Bromide yields not more than 0.15 percent of residue on ignition.

Assay—Dissolve about 800 mg. of Methantheline Bromide, accurately weighed, in 50 ml. of glacial acetic acid. Add 10 ml. of mercuric acetate T.S., and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 42.04 mg. of $C_{21}H_{26}BrNO_3$.

Packaging and storage—Preserve Methantheline Bromide in well-closed containers.

CATEGORY—Anticholinergic.
USUAL DOSE—**50 mg.** four times a day.
USUAL DOSE RANGE—**50** to **100 mg.**

Methantheline Bromide Tablets

Methantheline Bromide Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{21}H_{26}BrNO_3$.

Identification—Triturate a quantity of powdered Methantheline Bromide Tablets, equivalent to about 500 mg. of methantheline bromide, with 10 ml. of chloroform. Filter the mixture, and evaporate the filtrate to a thick oil with the aid of a current of air. Stir the residue with about 5 ml. of ether: a white powder is obtained which responds to the *Identification tests* under *Methantheline Bromide*, page 424.

Disintegration, page 878—The disintegration time limit for Methantheline Bromide Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Methantheline Bromide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Triturate a tablet with methanol in a glass mortar, and quantitatively transfer the mixture to a 100-ml. volumetric flask with the aid of methanol. Dilute to volume with methanol, mix, and filter, discarding the first 25 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol to provide a solution containing approximately 500 mcg. of methantheline bromide per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Methantheline Bromide Reference Standard, in the same medium, at a concentration of about 500 mcg. per ml., in 1-cm. cells, at the maximum at about 282 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{21}H_{26}BrNO_3$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of methantheline bromide, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of methantheline bromide in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Methantheline Bromide Tablets. Weigh accurately a portion of the powder, equivalent to about 800 mg. of methantheline bromide, and transfer to a medium-porosity, sintered-glass funnel that is fitted into a small suction flask.

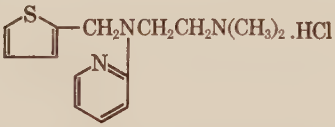
Wash the powder with 10 ml. of ether, stir with a small rod, and remove the ether by suction. Wash with two additional 10-ml. portions of ether, and discard the ether washings. In the same manner, extract the powder with four 10-ml. portions of chloroform. Transfer the combined chloroform extracts to a tared beaker, and evaporate carefully on a hot plate until only a heavy oil remains, avoiding local overheating. Cool, and dry the residue in vacuum for 15 minutes. Add 10 ml. of ether to the oily residue, and stir until the residue becomes a white, crystalline powder. Allow the solids to settle, and decant the clear liquid, avoiding loss of solid. Dry in air until the odor of ether is no longer perceptible, heat at 105° for 30 minutes, cool, and weigh. Continue as directed in the *Assay* under *Methantheline Bromide*, page 424.

Packaging and storage—Preserve Methantheline Bromide Tablets in well-closed containers.

Tablets available—Methantheline Bromide Tablets usually available contain the following amount of methantheline bromide: 50 mg.

CATEGORY and DOSE—See Methantheline Bromide.

Methapyrilene Hydrochloride



2-[[2-(Dimethylamino)ethyl]-2-thenylamino]pyridine Monohydrochloride

$C_{14}H_{19}N_3S.HCl$ Mol. wt. 297.85

Methapyrilene Hydrochloride, dried at 105° for 3 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{14}H_{19}N_3S.HCl$.

Description—Methapyrilene Hydrochloride occurs as a white, crystalline powder, usually having a faint odor. Its solutions are slightly acid to litmus, having a pH of about 5 to 6.

Solubility—Methapyrilene Hydrochloride is very soluble in water. It is freely soluble in alcohol and in chloroform. It is practically insoluble in ether and in benzene.

Identification—

A: Dissolve 25 mg. of Methapyrilene Hydrochloride in 5 ml. of sulfuric acid: a pronounced orange-brown color is produced, which changes to a greenish yellow upon dilution with 20 ml. of water, the solution acquiring a slight turbidity.

B: Methapyrilene Hydrochloride responds to the tests for *Chloride,* page 808

Melting range, page 814—Methapyrilene Hydrochloride melts between 161° and 165°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methapyrilene Hydrochloride, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Methapyrilene Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 40,000 solution of Methapyrilene Hydrochloride in 0.5 *N* sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Methapyrilene Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 313 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Methapyrilene Hydrochloride at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Selenium—A *Test Preparation* prepared with 100 mg. of Methapyrilene Hydrochloride and 100 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Residue on ignition, page 858—Methapyrilene Hydrochloride yields not more than 0.3 percent of residue on ignition.

Assay—Transfer to a beaker about 500 mg. of Methapyrilene Hydrochloride, previously dried at 105° for 3 hours and accurately weighed, and dissolve it in 80 ml. of glacial acetic acid. Add 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid, determining the endpoint potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 14.89 mg. of $C_{14}H_{19}N_3S.HCl$.

Packaging and storage—Preserve Methapyrilene Hydrochloride in tight, light-resistant containers.

Category—Antihistaminic.

Usual dose—**50 mg.** up to four times a day.

Usual dose range—**50** to **100 mg.**

Methapyrilene Hydrochloride Capsules

Methapyrilene Hydrochloride Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_{19}N_3S.HCl$.

Identification—

A: The solution prepared from Methapyrilene Hydrochloride Capsules as directed in the *Assay* exhibits an absorbance maximum at 313 ± 2 mμ.

B: A filtered solution of Methapyrilene Hydrochloride Capsules, equivalent to methapyrilene hydrochloride solution (1 in 20), responds to the tests for *Chloride*, page 808.

Content uniformity, *Method II*, page 798—Methapyrilene Hydrochloride Capsules meet the requirements of the content uniformity test for capsules, using the following special procedure: Quantitatively transfer the contents of a capsule as completely as possible to a 100-ml. volumetric flask. Rinse the empty capsule with about 5 ml. of alcohol, and add these rinsings to the flask. Add 50 ml. of water, and shake mechanically for 15 minutes. Dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with 0.1 N hydrochloric acid to provide a solution containing approximately 25 mcg. of methapyrilene hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Methapyrilene Hydrochloride Reference Standard, in the same medium, at a concentration of about 25 mcg. per ml., in 1-cm. cells, at the maximum at about 313 mμ, with a suitable spectrophotometer, using 0.1 N hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{14}H_{19}N_3S.HCl$ in the capsule by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of methapyrilene hydrochloride, in mg., in the capsule; D is the exact concentration, in mcg. per ml., of methapyrilene hydrochloride in the sample solution, based upon the labeled quantity per capsule and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Transfer, as completely as possible, the contents of not less than 20 Methapyrilene Hydrochloride Capsules to a suitable tared container, and weigh. Mix the powder thoroughly with a glass rod, and transfer an accurately weighed portion of the powder, equivalent to about 25 mg. of methapyrilene hydrochloride, to a 125-ml. separator. Proceed as directed under *Salts of Organic Nitrogenous Bases*, page 865, beginning with "Then to the separator add 20 ml. of 0.1 N sulfuric acid . . . ," and determining the absorbance at the maximum at about 313 mμ. Calculate the quantity, in mg., of $C_{14}H_{19}N_3S.HCl$ in the portion of the Capsules taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Methapyrilene Hydrochloride Reference Standard in the *Standard preparation*.

Packaging and storage—Preserve Methapyrilene Hydrochloride Capsules in tight containers.

Capsules available—Methapyrilene Hydrochloride Capsules usually available contain the following amounts of methapyrilene hydrochloride: 25, 50, and 100 mg.

Category and Dose—See Methapyrilene Hydrochloride.

Methapyrilene Hydrochloride Tablets

Methapyrilene Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{14}H_{19}N_3S.HCl$.

Identification—Extract a quantity of finely powdered Methapyrilene Hydrochloride Tablets, equivalent to about 25 mg. of methapyrilene hydrochloride, with two 5-ml. portions of chloroform. Filter the combined chloroform extracts, and evaporate to dryness: the residue so obtained responds to *Identification test A* under *Methapyrilene Hydrochloride*, page 426.

Disintegration, page 878—The disintegration time limit for Methapyrilene Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Methapyrilene Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

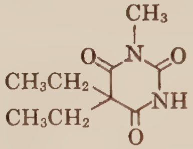
Assay—Proceed as directed under *Salts of Organic Nitrogenous Bases*, page 865, determining the absorbance at 313 mμ. Calculate the quantity, in mg., of $C_{14}H_{19}N_3S.HCl$ in the portion of the Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., calculated on the anhydrous basis, of NF Methapyrilene Hydrochloride Reference Standard in the *Standard preparation*.

Packaging and storage—Preserve Methapyrilene Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Methapyrilene Hydrochloride Tablets usually available contain the following amount of methapyrilene hydrochloride: 50 mg.

CATEGORY and DOSE—See Methapyrilene Hydrochloride.

Metharbital



5,5-Diethyl-1-methylbarbituric Acid

$C_9H_{14}N_2O_3$ Mol. wt. 198.22

Metharbital, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_9H_{14}N_2O_3$.

Description—Metharbital occurs as a white to nearly white, crystalline powder, possessing a faint aromatic odor. The pH of a saturated solution is about 6.

Solubility—Metharbital is slightly soluble in water. It is soluble in alcohol and sparingly soluble in ether.

Identification—Shake about 300 mg. of Metharbital with 5 ml. of 0.2 *N* sodium hydroxide for 2 minutes, filter, and to 1 ml. of the filtrate add several drops of silver nitrate T.S.: a white precipitate, soluble in ammonia T.S., is formed. To a second 1-ml. portion of the filtrate add several drops of mercuric chloride T.S.: a white precipitate, soluble in ammonia T.S., is formed.

Melting range, page 814—Metharbital melts between 151° and 155°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Metharbital, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Metharbital Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Metharbital in 0.1 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Metharbital Reference Standard similarly measured.

Water, page 900—Determine the water content of Metharbital by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Metharbital yields not more than 0.1 percent of residue on ignition.

Assay—Transfer to a 100-ml. volumetric flask about 100 mg. of Metharbital, previously dried at 105° for 4 hours and accurately weighed, add 0.1 *N* sodium hydroxide to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with 0.1 *N* sodium hydroxide, and mix. Transfer 10.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with 0.1 *N* sodium hydroxide, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Metharbital Reference Standard, in 0.1 *N* sodium hydroxide, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 244 mμ, with a suitable spectrophotometer, using 0.1 *N* sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_9H_{14}N_2O_3$ in the Metharbital taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Metharbital in tight containers.

Category—Anticonvulsant.

Usual dose—Initial, **100 mg.** up to three times a day.

Usual dose range—**100** to **800 mg.** per day.

Metharbital Tablets

Metharbital Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_9H_{14}N_2O_3$.

Identification—Extract with solvent hexane in a continuous extraction apparatus, an amount of powdered Metharbital Tablets, equivalent to about 500 mg. of metharbital. Dry the residue in the thimble, extract it with alcohol in the apparatus, evaporate the alcohol extract to dryness, and dry at 105° for 2 hours: a portion of the residue of metharbital so obtained responds to the *Identification tests* and the *Ultraviolet absorption test* under *Metharbital*, page 428.

Disintegration, page 878—The disintegration time limit for Metharbital Tablets is 10 minutes.

Weight variation, page 901—Metharbital Tablets meet the requirements of the weight variation test for tablets.

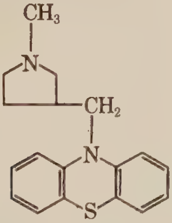
Assay—Weigh and finely powder not less than 20 Metharbital Tablets. Weigh accurately a portion of the powder, equivalent to about 100 mg. of metharbital, and transfer it to a 100-ml. volumetric flask. Add 50 ml. of 0.1 *N* sodium hydroxide, and shake mechanically for 15 minutes. Dilute to volume with 0.1 *N* sodium hydroxide, mix, and filter. Transfer 10.0 ml. of the filtrate to a second 100-ml. volumetric flask, dilute to volume with 0.1 *N* sodium hydroxide, and mix. Transfer 10.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with 0.1 *N* sodium hydroxide, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Metharbital Reference Standard, in 0.1 *N* sodium hydroxide, at a concentration of about 10 mcg. per ml. in 1-cm. cells, at the maximum at about 244 mμ, with a suitable spectrophotometer, using 0.1 *N* sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_9H_{14}N_2O_3$ in the portion of the Tablets taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Metharbital Tablets in tight containers.

Tablets available—Metharbital Tablets usually available contain the following amount of metharbital: 100 mg.

Category and Dose—See Metharbital.

Methdilazine*



10-[(1-Methyl-3-pyrrolidinyl)methyl]phenothiazine

$C_{18}H_{20}N_2S$ Mol. wt. 296.44

Methdilazine contains not less than 97.0 percent and not more than 103.0 percent of $C_{18}H_{20}N_2S$, calculated on the dried basis.

Description—Methdilazine occurs as a light tan, crystalline powder having a characteristic odor.

Solubility—Methdilazine is practically insoluble in water. It is freely soluble in diluted hydrochloric acid, and is soluble in alcohol and in chloroform.

Identification—Dissolve about 50 mg. of Methdilazine in 10 ml. of diluted hydrochloric acid in a test tube, add 3 ml. of buffered palladium chloride T.S. and 1 ml. of sodium lauryl sulfate solution (1 in 100), and mix: a blue color is formed.

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* Patented. See notice, page ii.

Melting range, page 814—Methdilazine melts within a range of 2° between 83° and 88°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methdilazine, previously dried in vacuum at 70° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Methdilazine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—Dissolve 25.0 mg. of Methdilazine in 25 ml. of 1 *N* hydrochloric acid, and dilute quantitatively and stepwise, with water, to a concentration of 5 mcg. per ml. The ultraviolet absorption spectrum of this solution exhibits maxima and minima at the same wavelengths as that of a 1 in 200,000 solution of NF Methdilazine Reference Standard in the same medium, similarly measured.

Loss on drying, page 814—Dry Methdilazine in vacuum at 70° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Methdilazine yields not more than 0.5 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 100 mg. of Methdilazine and 100 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test*, page 865, (30 parts per million).

Heavy metals, *Method II*, page 806—The heavy metals limit for Methdilazine is 20 parts per million.

Assay—Transfer about 100 mg. of Methdilazine, accurately weighed, to a 1000-ml. volumetric flask, dissolve in 100 ml. of 1 *N* hydrochloric acid, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methdilazine Reference Standard, in water at a concentration of about 5 mcg. per ml., in 1-cm. cells, at 252 mμ and at 275 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{18}H_{20}N_2S$ in the Methdilazine taken by the formula $20C \times (A_{U252} - A_{U275})/(A_{S252} - A_{S275})$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_{U252} and A_{U275} are the absorbances of the sample solution at 252 mμ and 275 mμ, respectively, and A_{S252} and A_{S275} are the absorbances of the Reference Standard solution at 252 mμ and 275 mμ, respectively.

Packaging and storage—Preserve Methdilazine in tight containers.

CATEGORY—Antipruritic.

USUAL DOSE—**7.2 mg.** (equivalent to 8 mg. of methdilazine hydrochloride) two to four times a day.

Methdilazine Tablets

Methdilazine Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{20}N_2S$.

Identification—Place in a mortar a number of Methdilazine Tablets, equivalent to about 20 mg. of methdilazine, add 10 ml. of ether, and grind thoroughly. Cool the mixture by evaporating a small amount of the ether in a stream of air, and filter. Again cool by evaporating a small amount of the ether. Filter if a precipitate forms. Evaporate the filtrate to dryness on a steam bath, dissolve the residue in about 3 ml. of chloroform, and transfer to a suitable mortar containing 500 mg. of potassium bromide. Grind thoroughly, dry under vacuum, repeat if necessary to remove the last trace of solvent, and prepare a pressed disk from the triturate. The infrared absorption spectrum of the potassium bromide dispersion exhibits maxima only at the same wavelengths as that of NF Methdilazine Reference Standard, similarly measured, in the 6 to 16-μ region.

Content uniformity, *Method I*, page 799—Methdilazine Tablets meet the requirements of the content uniformity test for tablets.

Disintegration, page 878—The disintegration time limit for Methdilazine Tablets is 30 minutes.

Assay—

Standard preparation—Transfer about 100 mg. of NF Methdilazine Reference Standard, accurately weighed, to a 250-ml. volumetric flask, add chloroform to volume, and mix.

Assay preparation—Weigh and finely powder not less than 20 Methdilazine Tablets, and transfer an accurately weighed portion of the powder, equivalent to about 40 mg. of methdilazine, to a 100-ml. volumetric flask. Add 60 ml. of chloroform, shake for 20 minutes, dilute to volume with chloroform, and mix. Filter, discarding the first 15 ml. of filtrate. Use the subsequent filtrate as directed in the *Procedure*.

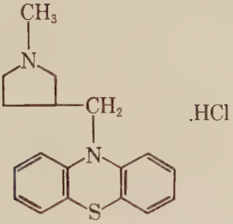
Procedure—Transfer 10.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 100-ml. volumetric flasks. To each flask add 20 ml. of chloroform and 4.0 ml. of buffered palladium chloride T.S., dilute to volume with alcohol, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 460 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{18}H_{20}N_2S$ in the portion of the Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Methdilazine Tablets in tight containers.

Tablets available—Methdilazine Tablets usually available contain the following amount of methdilazine: 3.6 mg.

CATEGORY and DOSE—See Methdilazine.

Methdilazine Hydrochloride*



10-[(1-Methyl-3-pyrrolidinyl)methyl]phenothiazine Monohydrochloride

$C_{18}H_{20}N_2S.HCl$ Mol. wt. 332.90

Methdilazine Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{18}H_{20}N_2S.HCl$, calculated on the dried basis.

Description—Methdilazine Hydrochloride occurs as a light tan, crystalline powder having a slight characteristic odor.

Solubility—Methdilazine Hydrochloride is freely soluble in water, in alcohol, and in chloroform.

Identification—

A: Dissolve about 50 mg. of Methdilazine Hydrochloride in 10 ml. of diluted hydrochloric acid in a test tube. Add 3 ml. of buffered palladium chloride T.S. and 1 ml. of sodium lauryl sulfate solution (1 in 100) and mix: a dark blue color is formed.

B: A solution of Methdilazine Hydrochloride responds to the tests for *Chloride,* page 808.

Melting range, page 814—Methdilazine Hydrochloride melts between 184° and 190°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methdilazine Hydrochloride, previously dried in vacuum at 70° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Methdilazine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Methdilazine Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Methdilazine Hydrochloride Reference Standard, similarly measured.

pH, page 824—The pH of a solution of Methdilazine Hydrochloride (1 in 100) is between 4.8 and 6.0.

Loss on drying, page 814—Dry Methdilazine Hydrochloride in vacuum at 70° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Methdilazine Hydrochloride yields not more than 0.5 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Methdilazine Hydrochloride is 20 parts per million.

Selenium—A *Test Preparation* prepared with 100 mg. of Methdilazine Hydrochloride and 100 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Assay—Transfer about 100 mg. of Methdilazine Hydrochloride, accurately weighed, to a 1000-ml. volumetric flask, add water to volume, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methdilazine Hydrochloride Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells, at 252 mμ and at 275 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{18}H_{20}N_2S.HCl$ in the portion of Methdilazine Hydrochloride taken by the formula $20C \times (A_{U252} - A_{U275})/(A_{S252} - A_{S275})$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_{U252} and A_{U275} are the absorbances of the sample solution at 252 mμ and 275 mμ, respectively, and A_{S252} and A_{S275} are the absorbances of the Reference Standard solution at 252 mμ and 275 mμ, respectively.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Methdilazine Hydrochloride in tight containers.

Category—Antipruritic.

Usual dose range—**8 mg.** two to four times a day.

Methdilazine Hydrochloride Syrup

Methdilazine Hydrochloride Syrup contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{20}N_2S.HCl$.

Identification—Transfer a volume of the Syrup, equivalent to about 4 mg. of methdilazine hydrochloride, to a 60-ml. separator, add 5 ml. of 0.1 *N* hydrochloric acid, and extract with 10 ml. of ether, discarding the extract. Add 10 ml. of sodium bicarbonate solution (1 in 10) to the separator, and extract with 3 ml. of chloroform. Filter the extract through a pledget of cotton. Evaporate the chloroform, carefully removing the last trace of solvent in a small vacuum flask. The infrared absorption spectrum of a potassium bromide dispersion of the methdilazine so obtained exhibits maxima at the same wavelengths as that of a similar preparation of NF Methdilazine Hydrochloride Reference Standard which has been treated in the same manner as the sample.

pH, page 824—The pH of Methdilazine Hydrochloride Syrup is between 3.3 and 4.1.

Assay—

Standard preparation—Transfer about 100 mg. of NF Methdilazine Hydrochloride Reference Standard, accurately weighed, to a 250-ml. volumetric flask, add chloroform to volume, and mix.

Assay preparation—Transfer a volume of Methdilazine Hydrochloride Syrup, equivalent to about 4 mg. of methdilazine hydrochloride, to a 60-ml. separator, add 10 ml. of a saturated solution of sodium chloride, and extract with three 10-ml. portions of chloroform, transferring each extract into a 100-ml. volumetric flask.

Procedure—Transfer 10.0 ml. of the *Standard preparation* to a 100-ml. volumetric flask, and add 20 ml. of chloroform. To this flask and to the flask containing the *Assay preparation* add 20 ml. of chloroform and 4.0 ml. of palladium chloride T.S., dilute to volume with alcohol, and mix. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 460 mμ with a suitable spectrophotometer, using a mixture of 30 ml. of chloroform, 4 ml. of water, and 66 ml. of alcohol as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{18}H_{20}N_2S.HCl$ in each ml. of the Syrup taken by the formula $0.01 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Methdilazine Hydrochloride Reference Standard in the *Standard preparation*, and V is the volume, in ml., of Syrup taken.

Alcohol content—Determine the alcohol content by the gas-liquid chromatographic procedure, page 772. Methdilazine Hydrochloride Syrup contains from 6.5 to 7.5 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Methdilazine Hydrochloride Syrup in tight, light-resistant containers.

Syrup available—Methdilazine Hydrochloride Syrup usually available contains the following amount of methdilazine hydrochloride: 4 mg. in 5 ml.

Category and Dose—See Methdilazine Hydrochloride.

Methdilazine Hydrochloride Tablets

Methdilazine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{20}N_2S.HCl$.

Identification—Transfer a portion of finely powdered Methdilazine Hydrochloride Tablets, equivalent to about 8 mg. of methdilazine hydrochloride, to a 60-ml. separator, add 10 ml. of sodium bicarbonate solution (1 in 10), and extract with 3 ml. of chloroform. Filter the extract through a pledget of cotton. Evaporate the chloroform, carefully removing the last trace of solvent in a small vacuum flask. The infrared absorption spectrum of a potassium bromide dispersion of the methdilazine so obtained exhibits maxima at the same wavelengths as that of a similar preparation of NF Methdilazine Hydrochloride Reference Standard, which has been treated in the same manner as the sample.

Disintegration, page 878—The disintegration time limit for Methdilazine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Methdilazine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Transfer about 100 mg. of NF Methdilazine Hydrochloride Reference Standard, accurately weighed, to a 250-ml. volumetric flask, add chloroform to volume, and mix.

Assay preparation—Weigh and finely powder not less than 20 Methdilazine Hydrochloride Tablets, and transfer an accurately weighed portion of the powder, equivalent to about 80 mg. of methdilazine, to a 200-ml. volumetric flask. Add 60 ml. of chloroform, shake for 20 minutes, dilute to volume with chloroform, and mix. Filter, discarding the first 15 ml. of filtrate. Use the subsequent filtrate as directed in the *Procedure*.

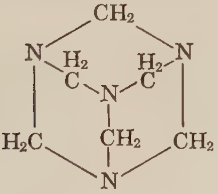
Procedure—Transfer 10.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 100-ml. volumetric flasks. To each flask add 20 ml. of chloroform and 4.0 ml. of buffered palladium chloride T.S., dilute to volume with alcohol, and mix. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 460 mμ with a suitable spectrophotometer, using water as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{18}H_{20}N_2S.HCl$ in the portion of the Tablets taken by the formula $0.2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Methdilazine Hydrochloride in the *Standard preparation*.

Packaging and storage—Preserve Methdilazine Hydrochloride Tablets in tight containers.

Tablets available—Methdilazine Hydrochloride Tablets usually available contain the following amount of methdilazine hydrochloride: 8 mg.

CATEGORY and DOSE—See Methdilazine Hydrochloride.

Methenamine



Hexamethylenetetramine

$C_6H_{12}N_4$ Mol. wt. 140.19

Methenamine, dried over phosphorus pentoxide for 4 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_6H_{12}N_4$.

Description—Methenamine occurs as colorless, lustrous crystals, or as a white, crystalline powder. It is practically odorless. When brought into contact with fire, it readily ignites, burning with a smokeless flame. It sublimes at about 260° without melting. Its solutions are alkaline to litmus.

Solubility—Methenamine is freely soluble in water. It is soluble in alcohol and in chloroform.

Identification—Heat a solution of Methenamine (1 in 10) with diluted sulfuric acid: formaldehyde is liberated, recognizable by its odor and by its darkening of paper moistened with silver ammonium nitrate T.S. On the subsequent addition of an excess of sodium hydroxide T.S. to the solution, ammonia is evolved.

Loss on drying, page 814—Dry Methenamine over phosphorus pentoxide for 4 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Methenamine yields not more than 0.05 percent of residue on ignition.

Chloride, page 784—One g. of Methenamine shows no more chloride than corresponds to 0.2 ml. of 0.02 *N* hydrochloric acid (0.014 percent).

Sulfate—To 10 ml. of a solution of Methenamine (1 in 50), acidified with 5 drops of hydrochloric acid, add 5 drops of barium chloride T.S.: no turbidity is produced within 1 minute.

Ammonium salts—To 10 ml. of a solution of Methenamine (1 in 20) add 1 ml. of alkaline mercuric-potassium iodide T.S.: the mixture is not darker in color than a mixture of 1 ml. of the reagent and 10 ml. of water.

Heavy metals, page 806—Dissolve 2 g. of Methenamine in 10 ml. of water, and add 2 ml. of diluted hydrochloric acid and water to make 25 ml. Continue as directed for *Solution B* under *Method I*, page 806, except use glacial acetic acid to adjust the pH: the heavy metals limit for Methenamine is 10 parts per million.

Assay—Transfer about 1 g. of Methenamine, previously dried over phosphorus pentoxide for 4 hours and accurately weighed, to a beaker. Add 40.0 ml. of 1 *N* sulfuric acid, and heat on a steam bath, adding water from time to time, if necessary, until the odor of formaldehyde is no longer perceptible. Cool, add 20 ml. of water, then add 3 drops of methyl red T.S., and titrate the excess acid with 1 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 1 *N* sulfuric acid is equivalent to 35.05 mg. of $C_6H_{12}N_4$.

Packaging and storage—Preserve Methenamine in well-closed containers.

CATEGORY—Antibacterial (urinary tract).

USUAL DOSE—**1 g.** four times a day.

USUAL DOSE RANGE—**500 mg.** to **1.5 g.**

Methenamine Tablets

Methenamine Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{12}N_4$.

Identification—Dissolve about 500 mg. of powdered Methenamine Tablets in 10 ml. of water, add 10 ml. of diluted sulfuric acid, and heat: formaldehyde is liberated, recognizable by its odor and by its darkening of paper moistened with silver ammonium nitrate T.S. On the subsequent addition of an excess of sodium hydroxide T.S. to the solution, ammonia is evolved.

Disintegration, page 878—The disintegration time limit for Methenamine Tablets is 30 minutes.

Weight variation, page 901—Methenamine Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Methenamine Tablets. Weigh accurately a portion of the powder, equivalent to about 1 g. of methenamine, and transfer it completely to a beaker. Add 40.0 ml. of 1 *N* sulfuric acid, and heat on a steam bath, adding water from time to time, if necessary, until the odor of formaldehyde is no longer perceptible. Cool, add 20 ml. of water, then add 3 drops of methyl red T.S., and titrate the excess acid with 1 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 1 *N* sulfuric acid is equivalent to 35.05 mg. of $C_6H_{12}N_4$.

Packaging and storage—Preserve Methenamine Tablets in well-closed containers.

Tablets available—Methenamine Tablets usually available contain the following amounts of methenamine: 300 and 500 mg.

CATEGORY and DOSE—See Methenamine.

Methenamine and Sodium Biphosphate Tablets

Methenamine and Sodium Biphosphate Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $C_6H_{12}N_4$ (methenamine) and of $NaH_2PO_4 . H_2O$ (sodium biphosphate).

Identification—

A: Powder several Methenamine and Sodium Biphosphate Tablets, and heat a filtered solution of the powder, equivalent to methenamine 1 in 10, with diluted sulfuric acid: it decomposes with the liberation of formaldehyde, recognizable by its odor, and by its darkening of paper moistened with silver ammonium nitrate T.S. On the subsequent addition of an excess of sodium hydroxide T.S. to the solution, ammonia is evolved.

B: Add 1 ml. of alkaline mercuric-potassium iodide T.S. to a filtered solution of Methenamine and Sodium Biphosphate Tablets, equivalent to methenamine 1 in 20: a yellow precipitate forms, and after acidification with hydrochloric acid, the precipitate becomes soluble upon the addition of ammonia T.S.

C: A filtered solution of Methenamine and Sodium Biphosphate Tablets, equivalent to sodium biphosphate 1 in 20, responds to the tests for *Sodium*, page 810, and for *Phosphate*, page 809.

Disintegration, page 878—The disintegration time limit for Methenamine and Sodium Biphosphate Tablets is 30 minutes.

Weight variation, page 901—Methenamine and Sodium Biphosphate Tablets meet the requirements of the weight variation test for tablets.

Ammonium salts—Dissolve 500 mg. of powdered Methenamine and Sodium Biphosphate Tablets in 10 ml. of water, add 5 ml. of sodium hydroxide T.S., and follow with 1 ml. of alkaline mercuric-potassium iodide T.S.: the color produced in 15 seconds may be yellow, but not orange-yellow or darker.

Assay for methenamine—Weigh and finely powder not less than 20 Methenamine and Sodium Biphosphate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 250 mg. of methenamine, to a 1-liter beaker. Add 200 ml. of water and 50 ml. of 1 *N* sulfuric acid, and boil the mixture gently until all of the formaldehyde has been driven off, adding water, if necessary, to maintain approximately the original volume. Cool the liquid, transfer to an 800-ml. Kjeldahl flask, add water to make the liquid measure about 300 ml., and add an excess of sodium hydroxide solution (1 in 2). Connect the flask to a distillation trap and condenser and distil the liberated ammonia into 25.0 ml. of 0.5 *N* sulfuric acid, taking care that the adapter dips beneath the surface of the acid, and that at least 250 ml. of distillate is collected. Add 3 drops of methyl red T.S. and titrate the excess acid with 0.5 *N* sodium hydroxide. Each ml. of 0.5 *N* sulfuric acid is equivalent to 17.52 mg. of $C_6H_{12}N_4$.

Assay for sodium biphosphate—Transfer an accurately weighed portion of finely powdered Methenamine and Sodium Biphosphate Tablets, equivalent to about 60 mg. of sodium biphosphate, into a 500-ml. Kjeldahl flask. Add 25 ml. of nitric acid and 10 ml. of sulfuric acid, and boil gently, adding additional nitric acid, if necessary, until all organic matter is destroyed. Cool, add 50 ml. of water, and boil vigorously until brown fumes cease to be evolved. Cool, transfer the contents of the Kjeldahl flask to a beaker, dilute to about 100 ml. with water, and neutralize the solution with ammonia T.S. To the neutralized solution add 10 g. of ammonium nitrate, heat to a temperature of 35° or 40°, and add 75 ml. of ammonium molybdate T.S. with stirring, and continue to stir the mixture for 15 minutes at room temperature. Allow the mixture to stand for about 15 minutes, and decant the supernatant liquid through a filter crucible. Wash the precipitate in the beaker by decantation with two 30-ml. portions of water, stirring thoroughly and allowing to settle before passing the supernatant liquid through the filter crucible. Transfer the precipitate to the filter, wash with cold water until the washings are neutral to litmus, place the crucible and contents in the beaker used for the precipitation, and add 50 ml. of water. Dissolve the yellow precipitate in an accurately measured excess of 0.5 *N* sodium hydroxide, add 3 drops of phenolphthalein T.S., and titrate the excess sodium hydroxide with 0.5 *N* sulfuric acid. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.5 *N* sodium hydroxide is equivalent to 3.000 mg. of $NaH_2PO_4 . H_2O$.

Packaging and storage—Preserve Methenamine and Sodium Biphosphate Tablets in tight containers.

Tablets available—Methenamine and Sodium Biphosphate Tablets usually available contain the following amounts of methenamine and sodium biphosphate: of each, 300 and 500 mg.

Category—Antibacterial (urinary tract).

Usual individual dose of methenamine and sodium biphosphate—**500 mg.** of each.

Methiodal, Sodium, page 650
Methiodal, Sodium, Injection, page 651

Methionine

$$CH_3SCH_2CH_2\underset{\underset{NH_2}{|}}{C}HCOOH$$

DL-2-Amino-4-(methylthio)butyric Acid

$C_5H_{11}NO_2S$ Mol. wt. 149.21

Methionine contains not less than 99.0 percent and not more than 100.5 percent of $C_5H_{11}NO_2S$, calculated on the dried basis.

Description—Methionine occurs as white, crystalline platelets or as a powder. It has a characteristic odor.

Solubility—Methionine is soluble in water. It is soluble in dilute acids and in solutions of alkali hydroxides. It is very slightly soluble in alcohol, and practically insoluble in ether.

Identification—

A: Add 25 mg. of dry Methionine to 1 ml. of a saturated solution of anhydrous cupric sulfate in sulfuric acid: a yellow color appears.

B: To a solution of Methionine (1 in 1000) add in succession, shaking after each addition, 1 ml. of 5 *N* sodium hydroxide, 1 ml. of aminoacetic acid solution (1 in 100), and 0.3 ml. of freshly prepared sodium nitroprusside solution (1 in 10). Keep the mixture at about 40° for 10 minutes, cool in an ice bath for 2 minutes, then add 2 ml. of 20 percent hydrochloric acid and shake the mixture: a reddish purple color appears.

C: To 1 ml. of a 1 in 30 solution of Methionine add 1 ml. of ninhydrin T.S. and 100 mg. of sodium acetate, and heat to boiling: an intense violet-blue color is formed (*distinction from hydroxyl analog*).

pH, page 824—The pH of a solution of Methionine (1 in 100) is between 5.6 and 6.1.

Clarity and color of solution—Dissolve 450 mg. of Methionine in 15 ml. of water: the solution is clear and colorless.

Loss on drying, page 814—Dry Methionine at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Methionine yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—A 750-mg. portion of Methionine shows no more chloride than corresponds to 0.2 ml. of 0.02 *N* hydrochloric acid (0.019 percent).

Sulfate, page 784—A 750-mg. portion of Methionine shows no more sulfate than corresponds to 0.4 ml. of 0.02 *N* sulfuric acid (0.05 percent).

Selenium—A *Test Preparation* prepared with 200 mg. of Methionine meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Heavy metals, *Method II,* page 806—The heavy metals limit for Methionine is 20 parts per million.

Iron—Dissolve 1 g. of Methionine in 40 ml. of water, add 2 ml. of hydrochloric acid and about 50 mg. of ammonium persulfate, dilute to 50 ml., and mix. To this solution add 3 ml. of ammonium thiocyanate T.S., and mix thoroughly: the color obtained is no darker than that produced in 50 ml. of a solution containing 70 mcg. of ferrous ammonium sulfate (equivalent to 10 mcg. of Fe) when treated in the same manner. Methionine contains not more than 10 parts per million of Fe.

Assay—Transfer about 300 mg. of Methionine, accurately weighed, to a glass-stoppered flask. Add 100 ml. of water, 5 g. of dibasic potassium phosphate, 2 g. of monobasic potassium phosphate, and 2 g. of potassium iodide, and mix to dissolve. Add 50.0 ml. of 0.1 *N* iodine, stopper the flask, mix, and allow to stand for 30 minutes. Titrate the excess iodine with 0.1 *N* sodium thiosulfate. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 0.1 *N* iodine is equivalent to 7.461 mg. of $C_5H_{11}NO_2S$.

Packaging and storage—Preserve Methionine in well-closed, light-resistant containers.

CATEGORY—Lipotropic.

USUAL DOSE—**3 g.** one to three times a day.

USUAL DOSE RANGE—**3** to **20 g.** per day.

Methionine Capsules

Methionine Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_5H_{11}NO_2S$.

Identification—Macerate the contents of a sufficient number of Methionine Capsules, equivalent to about 100 mg. of methionine, in 100 ml. of water, and filter the solution. The solution responds to *Identification test B* under *Methionine,* page 435.

Weight variation, page 901—Methionine Capsules meet the requirements of the weight variation test for capsules.

Assay—Transfer, as completely as possible, the contents of not less than 20 Methionine Capsules into a 1000-ml. volumetric flask. Wash the emptied capsules with cold water and transfer the washings to the flask. Add water to volume, and mix. Filter, if necessary, through a dry filter into a dry flask, rejecting the first 20 ml. of the filtrate. Transfer to a glass-stoppered flask an accurately measured volume of the filtrate, equivalent to about 300 mg. of methionine. Add a sufficient amount of water to make the volume about 100 ml., and 5 g. of dibasic potassium phosphate, 2 g. of monobasic potassium phosphate, and 2 g. of potassium iodide, and mix to dissolve. Add 50.0 ml. of 0.1 *N* iodine, stopper the flask, mix, and allow to stand for 30 minutes. Titrate the excess iodine with 0.1 *N* sodium thiosulfate. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* iodine is equivalent to 7.461 mg. of $C_5H_{11}NO_2S$.

Packaging and storage—Preserve Methionine Capsules in well-closed, light-resistant containers.

Capsules available—Methionine Capsules usually available contain the following amounts of methionine: 200 and 500 mg.

CATEGORY and DOSE—See Methionine.

Methionine Tablets

Methionine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_5H_{11}NO_2S$.

Identification—A filtered solution of Methionine Tablets, representing a concentration of approximately 1 in 1000 of methionine, responds to *Identification test B* under *Methionine*, page 435.

Disintegration, page 878—The disintegration time limit for Methionine Tablets is 30 minutes in simulated gastric fluid T.S.

Weight variation, page 901—Methionine Tablets meet the requirements of the weight variation test for tablets.

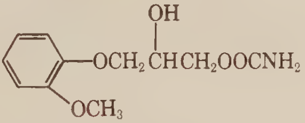
Assay—Weigh and finely powder not less than 20 Methionine Tablets. Weigh accurately a portion of the powder, equivalent to about 600 mg. of methionine, and transfer it completely to a 100-ml. volumetric flask. Add about 75 ml. of water, and allow to stand for 30 minutes with occasional swirling. Add water to volume, and mix. Filter, if necessary, through a dry filter into a dry flask, rejecting the first 20 ml. of the filtrate, and proceed as directed in the *Assay* under *Methionine Capsules*, page 436, beginning with "Transfer to a glass-stoppered flask an accurately measured volume of the filtrate . . . ."

Packaging and storage—Preserve Methionine Tablets in well-closed, light-resistant containers.

Tablets available—Methionine Tablets usually available contain the following amounts of methionine: 250 and 500 mg.

CATEGORY and DOSE—See Methionine.

Methocarbamol*



3-(*o*-Methoxyphenoxy)-1,2-propanediol 1-Carbamate

$C_{11}H_{15}NO_5$ Mol. wt. 241.25

Methocarbamol contains not less than 98.0 percent and not more than 102.0 percent of $C_{11}H_{15}NO_5$.

Description—Methocarbamol occurs as a white powder. It is odorless or has a slight characteristic odor.

Solubility—Methocarbamol is sparingly soluble in water and in chloroform. It is freely soluble in alcohol, and is insoluble in benzene and in *n*-hexane.

Melting range, page 814—Methocarbamol melts between 93° and 97°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methocarbamol, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Methocarbamol Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 25,000 solution of Methocarbamol in alcohol exhibits maxima and minima at the same wavelengths as that of NF Methocarbamol Reference Standard, similarly measured.

Residue on ignition, page 858—Methocarbamol yields not more than 0.1 percent of residue on ignition.

Heavy metals, page 806—Dissolve 500 mg. of Methocarbamol in a mixture of 23 ml. of water and 2 ml. of diluted acetic acid: the heavy metals limit for Methocarbamol is 20 parts per million.

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* Patented. See notice, page ii.

Assay—Transfer about 100 mg. of Methocarbamol, accurately weighed, to a 100-ml. volumetric flask, add alcohol to volume, and mix. Transfer 4.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methocarbamol Reference Standard in alcohol, at a concentration of about 40 mcg. per ml., in 1-cm. cells, at the maximum at about 274 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{11}H_{15}NO_5$ in the Methocarbamol taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Methocarbamol in tight containers.

Category—Skeletal muscle relaxant.

Usual dose range—Oral, **1.5** to **2 g.** four times a day for the first 2 or 3 days, then **1 g.** four times daily; intramuscular, **1 g.** every 8 hours; intravenous, **1** to **3 g.** per day given at a rate not exceeding 3 ml. per minute.

Methocarbamol Injection

Methocarbamol Injection is a sterile solution of methocarbamol in an aqueous solution of polyethylene glycol 300. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{11}H_{15}NO_5$.

Identification—Mix a volume of Methocarbamol Injection, equivalent to about 500 mg. of methocarbamol, with 15 ml. of water in a small glass-stoppered flask, freeze the solution, and allow to warm to room temperature. Remove and recrystallize a portion of the crystals, and dry at 50° for 3 hours: the methocarbamol so obtained melts between 93° and 97°, page 814.

pH, page 824—The pH of Methocarbamol Injection is between 4.0 and 5.0.

Aldehydes—Transfer to a 25-ml. volumetric flask an accurately measured volume of Methocarbamol Injection, equivalent to 400 mg. of methocarbamol, add 2.0 ml. of a filtered solution of phenylhydrazine in alcohol (1 in 100), and allow to stand for 10 minutes. Add 1 ml. of potassium ferricyanide solution (1 in 100), and allow to stand for 5 minutes. Add 4 ml. of hydrochloric acid, dilute to volume with alcohol, and mix. Determine the absorbance of this solution in a 1-cm. cell, with a suitable spectrophotometer, at the maximum at about 515 mμ, using a reagent blank to set the instrument: the absorbance if not greater than that produced by 4 ml. of a 1 in 100,000 solution of formaldehyde similarly measured (100 parts per million, w/w, as formaldehyde).

Other requirements—Methocarbamol Injection meets the requirements under *Injections*, page 810.

Assay—

Standard preparation—Transfer about 500 mg. of NF Methocarbamol Reference Standard, accurately weighed, to a separator, and dissolve in 5.0 ml. of a mixture of equal volumes of polyethylene glycol 300 and water, and continue as directed under *Assay preparation*, beginning with "... and extract with five 20-ml. portions of chloroform."

Assay preparation—Transfer to a separator an accurately measured volume of Methocarbamol Injection, equivalent to about 500 mg. of methocarbamol, and extract with five 20-ml. portions of chloroform. Filter the extracts through anhydrous sodium sulfate into a beaker, evaporate to a volume of about 10 ml., and cool. Quantitatively transfer, with the aid of chloroform, to a 25-ml. volumetric flask, dilute to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbances of the solutions in 0.1-mm. cells at 5.78 μ, with a suitable infrared spectrophotometer, using chloroform in a matched cell as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{11}H_{15}NO_5$ in each ml. of the Injection taken by the formula $25 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Methocarbamol Injection in single-dose containers, preferably of Type I glass.

Injection available—Methocarbamol Injection usually available contains the following amount of methocarbamol: 1 g. in 10 ml.

Category and Dose—See Methocarbamol.

Methocarbamol Tablets

Methocarbamol Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{11}H_{15}NO_5$.

Identification—Mix a portion of finely powdered Methocarbamol Tablets, equivalent to about 1 g. of methocarbamol, with 25 ml. of water in a separator, and extract with 25 ml. of chloroform. Filter the extract, and evaporate to dryness: the residue of methocarbamol so obtained melts between 93° and 97°, page 814.

Disintegration, page 878—The disintegration time limit for Methocarbamol Tablets, using simulated gastric fluid T.S. as the test medium in place of water, is 30 minutes.

Weight variation, page 901—Methocarbamol Tablets meet the requirements of the weight variation test for tablets.

Assay—

Standard preparation—Transfer about 400 mg. of NF Methocarbamol Reference Standard to a 25-ml. volumetric flask, add a 1 in 50 mixture of dimethylsulfoxide in chloroform to volume, and mix.

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 250-mm. tube to which is fused a 5-cm. length of 7-mm. tubing) with the aid of a tamping rod about 45 cm. in length and having a disk with a diameter about 1 mm. less than that of the tube. To 2 g. of purified siliceous earth in a 100-ml. beaker add 1-ml. of water, and mix until a uniform, fluffy mixture is obtained. Transfer to the tube, and tamp gently to compress the mixture to a uniform mass.

Assay preparation—Weigh and finely powder not less than 20 Methocarbamol Tablets. Transfer to a 100-ml. beaker an accurately weighed portion of the powder, equivalent to about 400 mg. of methocarbamol, add 0.5 ml. of dimethyl sulfoxide, and mix with a spatula until the powder is thoroughly wetted. Add 3 g. of purified siliceous earth and 1 ml. of water, mix as directed under *Chromatographic column,* and transfer quantitatively to the column in two portions. Scrub the beaker with several small portions of purified siliceous earth, transfer the scrubbings to the column, and tamp gently. Elute the methocarbamol with 40 ml. of water-washed chloroform, passing the eluate through anhydrous sodium sulfate into a 25-ml. volumetric flask. Dilute to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbance of the *Standard preparation* and of the *Assay preparation* in 0.1-mm. cells, at the maximum at about 5.78 μ, with a suitable spectrophotometer, using a 1 in 50 mixture of dimethyl sulfoxide in chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{11}H_{15}NO_5$ in the portion of Tablets taken by the formula $25C \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation.*

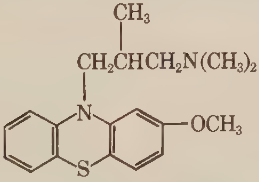
Packaging and storage—Preserve Methocarbamol Tablets in tight containers.

Tablets available—Methocarbamol Tablets usually available contain the following amounts of methocarbamol: 500 and 750 mg.

CATEGORY and DOSE—See Methocarbamol.

Methohexital, Sodium, for Injection, page 651

Methotrimeprazine*



(−)-10-[3-(Dimethylamino)-2-methylpropyl]-2-methoxyphenothiazine

$C_{19}H_{24}N_2OS$ Mol. wt. 328.48

Methotrimeprazine contains not less than 98.0 percent and not more than 101.0 percent of $C_{19}H_{24}N_2OS$, calculated on the dried basis.

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* Patented. See notice, page ii.

Description—Methotrimeprazine occurs as a fine, white, practically odorless, crystalline powder. It melts at about 126°.

Solubility—Methotrimeprazine is practically insoluble in water, sparingly soluble in mthanol, and freely soluble in chloroform and in ether. It is sparingly soluble in alcohol at 25° but is freely soluble in boiling alcohol.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methotrimeprazine, previously dried at 100° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Methotrimeprazine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 62,500 solution of Methotrimeprazine in alcohol exhibits maxima and minima at the same wavelengths as that of NF Methotrimeprazine Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 255 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Methotrimeprazine, calculated on the dried basis, determined in a chloroform solution containing 500 mg. of Methotrimeprazine in each 10 ml., is between −15° and −18°.

Loss on drying, page 814—Dry Methotrimeprazine at 100° for 3 hours; it loses not more than 0.5 percent of its weight.

Selenium—A *Test Preparation* prepared with 100 mg. of Methotrimeprazine and 100 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Assay—Dissolve about 700 mg. of Methotrimeprazine, accurately weighed, in 100 ml. of chloroform, add 1 drop of a 1 in 500 solution of crystal violet in chloroform, and titrate with 0.1 *N* perchloric acid in glacial acetic acid to the first disappearance of the violet tinge. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 32.85 mg. of $C_{19}H_{24}N_2OS$.

Packaging and storage—Preserve Methotrimeprazine in well-closed, light-resistant containers.

CATEGORY—Analgesic.

USUAL DOSE—Intramuscular, **10** to **30 mg.** every 4 to 6 hours.

USUAL DOSE RANGE—**5** to **40 mg.**

Methotrimeprazine Injection

Methotrimeprazine Injection is a sterile solution of methotrimeprazine in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{19}H_{24}N_2OS$.

Identification—Transfer 1.0 ml. of Methotrimeprazine Injection to a 125-ml. separator and add sodium hydroxide T.S., dropwise, until the solution becomes opaque white. Extract with 50 ml. of ether, wash the ether extract with 25 ml. of water, and discard the washing. Filter the ether extract through a layer of anhydrous sodium sulfate into a beaker, and evaporate the filtrate to complete dryness by means of a stream of nitrogen: the infrared absorption spectrum of a potassium bromide dispersion prepared from the residue so obtained exhibits maxima at the same wavelengths as that of NF Methotrimeprazine Reference Standard, similarly measured.

pH, page 824—The pH of Methotrimeprazine Injection is between 3.0 and 5.0.

Other requirements—Methotrimeprazine Injection meets the requirements under *Injections,* page 810.

Assay—[Note: Use low-actinic glassware.]

Phosphate buffer, pH 5.3—Dissolve 38.0 g. of monobasic sodium phosphate and 2.0 g. of anhydrous dibasic sodium phosphate in water, dilute to 1000 ml., and mix.

Bromocresol green solution—Dissolve 200 mg. of bromocresol green in a mixture of 6.4 ml. of 0.1 *N* sodium hydroxide and 100 ml. of water. Dilute to 250 ml. with water, extract with five 25-ml. portions of chloroform, discard the extracts, and filter the aqueous phase.

Standard preparation—Weigh accurately about 40 mg. of NF Methotrimeprazine Reference Standard, and dissolve in sufficient water to make 500.0 ml., warming gently to effect solution.

Assay preparation—Transfer an accurately measured volume of Methotrimeprazine Injection, equivalent to about 40 mg. of methotrimeprazine, to a 500-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Pipet 6.0 ml. each of the *Assay preparation* and of the *Standard preparation* into separate 125-ml. separators. To each separator add 5 ml. of *Bromocresol green solution* and 10 ml. of *pH 5.3 Phosphate buffer.* Extract with three 25-ml. portions of chloroform, filtering the extracts from each separator into separate 100-ml. volumetric flasks. Dilute the filtrate in each flask to volume with chloroform, and mix. Concomitantly determine the absorbance of the solutions, in 1-cm. cells, at the maximum at about 415 mμ, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{19}H_{24}N_2OS$ in each ml. of the Injection taken by the formula $0.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Methotrimeprazine Injection in single-dose or multiple-dose containers, preferably of Type I glass, protected from light.

Injection available—Methotrimeprazine Injection usually available contains the following amount of methotrimeprazine: 20 mg. in 1 ml.

CATEGORY and DOSE—See Methotrimeprazine.

Methoxyflurane*

$CHCl_2CF_2—O—CH_3$

2,2-Dichloro-1,1-difluoroethyl Methyl Ether

$C_3H_4Cl_2F_2O$ Mol. wt. 164.97

Methoxyflurane contains not less than 99.9 percent and not more than 100.0 percent of $C_3H_4Cl_2F_2O$. It may contain a suitable stabilizer.

Description—Methoxyflurane is a clear, practically colorless, mobile liquid, having a characteristic odor. It boils at about 105°.

Solubility—Methoxyflurane is miscible with alcohol, with acetone, with chloroform, with ether, with benzene, and with fixed oils.

Identification—

A: To 1 ml. of Methoxyflurane in a test tube add 1 ml. of sulfuric acid: the sample forms a layer over the acid (*distinction from halothane*).

B: Cautiously heat the contents of the test tube from *Identification test A* with agitation: the interface disappears, and hydrofluoric acid is evolved (*distinction from chloroform, trichloroethylene, and halothane*).

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 20 solution of Methoxyflurane in chloroform exhibits maxima only at the same wavelengths as that of NF Methoxyflurane Reference Standard, similarly measured.

Specific gravity, page 866—The specific gravity of Methoxyflurane is between 1.420 and 1.425.

Nonvolatile residue—Allow 50 ml. of Methoxyflurane to evaporate at room temperature in a tared evaporating dish, and dry the residue at 105° for 1 hour: the weight of the residue does not exceed 1 mg.

Acidity—Shake 25 ml. of Methoxyflurane with 25 ml. of carbon dioxide-free water for 2 minutes, and allow the layers to separate. Add 1 drop of methyl red T.S. to the water extract, boil for 1 minute, and titrate with 0.01 N sodium hydroxide: not more than 0.5 ml. of 0.01 N sodium hydroxide is required to produce a distinct yellow color.

Foreign odor—Place 10 ml. of Methoxyflurane in a small, dry evaporating dish, and allow it to evaporate spontaneously to about 1 ml.: no foreign odor is perceptible during the evaporation. Pour the residue onto odorless filter paper: no foreign odor is perceptible as the last portions disappear from the paper.

Assay—Inject 30 μl. of Methoxyflurane into a suitable gas chromatograph (page 787) equipped with a thermal conductivity detector. Under typical conditions, the instrument contains a 3 m. × 6-mm. (outside diameter) stainless steel column packed with di(2-ethylhexyl)sebacate, 20 percent on purified siliceous earth; the column is maintained at a temperature of 100° to 110°; the injection port is maintained at 150°; and helium is used as the carrier gas at a flow rate of about 60 ml. per minute. From the area under the curve, calculate the percent (a/a) of $C_3H_4Cl_2F_2O$ in the sample taken.

Packaging and storage—Preserve in tight, light-resistant containers, and avoid exposure to excessive heat.

CATEGORY—General anesthetic.

APPLICATION—By inhalation as required.

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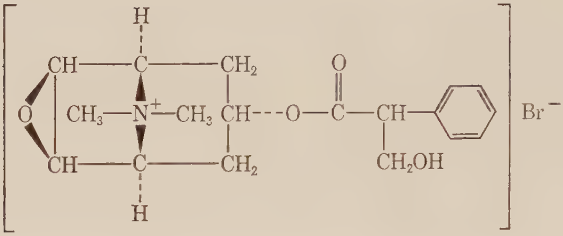
* Patented. See notice, page ii.

Methscopolamine Bromide



6β,7β-Epoxy-3α-hydroxy-8-methyl-1αH,5αH-tropanium Bromide (−)-Tropate

$C_{18}H_{24}BrNO_4$ Mol. wt. 398.30

Methscopolamine Bromide contains not less than 98.0 percent and not more than 101.0 percent of $C_{18}H_{24}BrNO_4$, calculated on the dried basis.

Description—Methscopolamine Bromide occurs as white crystals, or as a white, odorless, crystalline powder. When tested by the method under *Class Ia*, page 815, it melts at about 225° with decomposition.

Solubility—Methscopolamine Bromide is freely soluble in water, slightly soluble in alcohol, and insoluble in acetone and in chloroform.

Identification—

A: Dissolve about 5 mg. of Methscopolamine Bromide in 5 ml. of water, add 3 drops of ammonium reineckate T.S., and allow to stand for 5 minutes: a red precipitate is formed.

B: A solution of Methscopolamine Bromide (1 in 20) responds to the test for *Bromide*, page 808.

Specific rotation, page 822—The specific rotation of Methscopolamine Bromide, calculated on the dried basis, determined in a solution containing 500 mg. of Methscopolamine Bromide in each 10 ml., is between −21° and −25°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methscopolamine Bromide, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Methscopolamine Bromide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 1000 solution of Methscopolamine Bromide in alcohol exhibits maxima and minima at the same wavelengths as that of NF Methscopolamine Bromide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 257 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Methscopolamine Bromide at 105° for 3 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Methscopolamine Bromide yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 750 mg. of Methscopolamine Bromide, accurately weighed, in a mixture of 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., warming slightly to effect solution. Cool to room temperature, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 39.83 mg. of $C_{18}H_{24}BrNO_4$.

Packaging and storage—Preserve Methscopolamine Bromide in tight, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE—Oral, **2.5 mg.** four times a day. Parenteral, **500 mcg.** up to four times a day.

USUAL DOSE RANGE—Oral, **2.5 to 5 mg.**; parenteral, **250 mcg.** to **1 mg.**

Methscopolamine Bromide Injection

Methscopolamine Bromide Injection is a sterile solution of methscopolamine bromide in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{18}H_{24}BrNO_4$.

Identification—Methscopolamine Bromide Injection responds to the *Identification tests* under *Methscopolamine Bromide,* page 442.

pH, page 824—The pH of Methscopolamine Bromide Injection is between 4.5 and 6.0.

Other requirements—Methscopolamine Bromide Injection meets the requirements under *Injections,* page 810.

Assay—

Standard preparation—Dissolve in water a suitable quantity of NF Methscopolamine Bromide Reference Standard, previously dried at 105° for 3 hours and accurately weighed, and prepare, by stepwise and quantitative dilution, a solution in water containing about 50 mcg. per ml.

Assay preparation—Transfer an accurately measured volume of Methscopolamine Bromide Injection, equivalent to about 5 mg. of methscopolamine bromide, to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Pipet 10.0 ml. of the *Assay preparation* and 10.0 ml. of the *Standard preparation* into separate separators, and pipet 10.0 ml. of water into a third separator to serve as the blank. Add to each separator 10.0 ml. of pH 7.3 (±0.1) dye-buffer solution (consisting of 200 mg. of bromothymol blue in 3.2 ml. of 0.1 *N* sodium hydroxide, 577.5 mg. of citric acid monohydrate, and 6.317 g. of anhydrous dibasic sodium phosphate, in sufficient water to make 500.0 ml.), and mix. Completely extract the dye-complex from each separator using four 20-ml. portions of chloroform, filtering each extract through chloroform-washed cotton into a 100-ml. volumetric flask. Add chloroform to volume, and mix. Concomitantly determine the absorbances of the solutions obtained from the *Assay preparation* and *Standard preparation,* respectively, at the maximum at about 420 mμ, in 2-cm. capped cells with a suitable spectrophotometer, using the blank to set the instrument. Calculate the quantity, in mg., of $C_{18}H_{24}BrNO_4$ in each ml. of the Injection taken by the formula $0.1 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Methscopolamine Bromide Reference Standard in the *Standard preparation,* A_U is the absorbance of the solution from the *Assay preparation,* A_S is the absorbance of the solution from the *Standard preparation,* and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Methscopolamine Bromide Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injection available—Methscopolamine Bromide Injection usually available contains the following amount of methscopolamine bromide: 1 mg. in 1 ml.

CATEGORY and DOSE—See Methscopolamine Bromide.

Methscopolamine Bromide Tablets

Methscopolamine Bromide Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{24}BrNO_4$.

Identification—Powder a number of Methscopolamine Bromide Tablets equivalent to about 5 mg. of methscopolamine bromide, digest with 5 ml. of water for 10 minutes, and filter: the clear solution so obtained responds to the *Identification tests* under *Methscopolamine Bromide,* page 442.

Disintegration, page 878—The disintegration time limit for Methscopolamine Bromide Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Methscopolamine Bromide Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Methscopolamine Bromide Injection,* page 442.

Assay preparation—Weigh and finely powder not less than 10 Methscopolamine Bromide Tablets. Weigh accurately a portion of the powder, equivalent to about 5 mg. of methscopolamine bromide, and transfer completely, with the aid of 30 ml. of water, to a 100-ml. volumetric flask. Add water to volume, mix, and filter through a dry paper into a dry flask rejecting the first 10 ml. of filtrate.

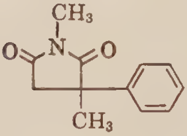
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Methscopolamine Bromide Injection,* page 442. Calculate the quantity, in mg., of $C_{18}H_{24}BrNO_4$ in the portion of the Tablets taken by the formula $0.1C \times (A_U/A_S)$.

Packaging and storage—Preserve Methscopolamine Bromide tablets in tight containers.

Tablets available—Methscopolamine Bromide Tablets usually available contain the following amount of methscopolamine bromide: 2.5 mg.

CATEGORY and DOSE—See Methscopolamine Bromide.

Methsuximide*



N,2-Dimethyl-2-phenylsuccinimide

$C_{12}H_{13}NO_2$ Mol. wt. 203.24

Methsuximide contains not less than 97.0 percent and not more than 103.0 percent of $C_{12}H_{13}NO_2$, calculated on the dried basis.

Description—Methsuximide occurs as a white to grayish white, crystalline powder. It is odorless or has not more than a slight odor.

Solubility—Methsuximide is slightly soluble in hot water, is freely soluble in alcohol and in ether, and is very soluble in chloroform.

Melting range, page 814—Methsuximide melts between 50° and 56°, by a *Class I* procedure, except that the sample is inserted into the bath at about room temperature.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methsuximide, previously dried over phosphorus pentoxide for 16 hours, exhibits maxima only at the same wavelengths as that of NF Methsuximide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 3000 solution of Methsuximide in alcohol exhibits maxima and minima at the same wavelengths as that of NF Methsuximide Reference Standard, similarly measured.

Loss on drying, page 814—Dry Methsuximide over phosphorus pentoxide for 16 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Methsuximide yields not more than 0.2 percent of residue on ignition.

Cyanide—Dissolve 1 g. of Methsuximide in 10 ml. of alcohol, and add 3 drops of ferrous sulfate T.S., 1 ml. of sodium hydroxide T.S., and a few drops of ferric chloride T.S. Warm gently, and finally acidify with diluted sulfuric acid: no blue precipitate or blue color is developed within 15 minutes.

Assay—Transfer about 150 mg. of Methsuximide, accurately weighed, to a 50-ml. volumetric flask, dissolve in 40 ml. of alcohol, then dilute to volume with alcohol, and mix. Transfer 5.0 ml. of this solution to a second 50-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methsuximide Reference Standard, in the same medium at a concentration of about 300 mcg. per ml., in 1-cm. cells, at the maximum at about 247 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{12}H_{13}NO_2$ in the Methsuximide taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Methsuximide in tight containers.

CATEGORY—Anticonvulsant.

USUAL DOSE—Initial, **300 mg.** daily. Maintenance range, **300 mg.** to **1.2 g.** daily.

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* Patented. See notice, page ii.

Methsuximide Capsules

Methsuximide Capsules contain not less than 92.0 percent and not more than 108.0 percent of the labeled amount of $C_{12}H_{13}NO_2$.

Identification—Mix a portion of the contents of Methsuximide Capsules, equivalent to about 200 mg. of methsuximide, with 25 ml. of water in a separator, extract with 50 ml. of ether, and discard the aqueous layer. Wash the ether extract with 25 ml. of water, and discard the water. Filter the extract, evaporate to dryness using a current of warm air, and dry the residue over phosphorus pentoxide for 16 hours. The residue so obtained meets the requirements for *Infrared absorption* under *Methsuximide,* page 444.

Weight variation, page 901—Methsuximide Capsules meet the requirements of the weight variation test for capsules.

Assay—Transfer, as completely as possible, the contents of not less than 20

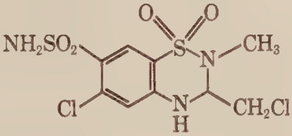
Methsuximide Capsules to a suitable tared container, and weigh. Mix thoroughly with a glass rod. Weigh accurately a portion of the powder, equivalent to about 300 mg. of methsuximide, and transfer to a 125-ml. separator. Add 20 ml. of water, and extract with three 40-ml. portions of chloroform, filtering each successive chloroform extract through a chloroform-washed pledget of cotton into a 150-ml. extraction flask. Evaporate the combined chloroform extracts on a steam bath to about 3 ml., then allow the remaining chloroform to evaporate at room temperature. Dissolve the residue of methsuximide in 30 ml. of alcohol, transfer quantitatively to a 100-ml. volumetric flask, and dilute to volume with alcohol. Pipet 5.0 ml. of the solution into a 50-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methsuximide Reference Standard, in the same medium at a concentration of about 300 mcg. per ml., in 1-cm. cells, at the maximum at about 247 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{12}H_{13}NO_2$ in the portion of Capsules taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Methsuximide Capsules in tight containers. Avoid excessive heat.

Capsules available—Methsuximide Capsules usually available contain the following amounts of methsuximide: 150 and 300 mg.

CATEGORY and DOSE—See Methsuximide.

Methyclothiazide*



6-Chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide

$C_9H_{11}Cl_2N_3O_4S_2$ Mol. wt. 360.24

Methyclothiazide contains not less than 97.0 percent and not more than 102.0 percent of $C_9H_{11}Cl_2N_3O_4S_2$, calculated on the dried basis.

Description—Methyclothiazide occurs as a white or practically white, crystalline powder. It is odorless or has a slight odor.

Solubility—Methyclothiazide is slightly soluble in alcohol, and is very slightly soluble in water, in chloroform, and in benzene. It is freely soluble in acetone and in pyridine, and is sparingly soluble in methanol.

Identification—Fuse about 100 mg. of Methyclothiazide with a pellet of sodium hydroxide: the ammonia fumes produced turn moistened red litmus paper blue. The fusion mixture responds to the test for *Sulfite*, page 810.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methyclothiazide, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Methyclothiazide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Methyclothiazide in methanol exhibits maxima and minima at the same wavelengths as that of NF Methyclothiazide Reference Standard, similarly measured.

Loss on drying, page 814—Dry Methyclothiazide at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Methyclothiazide yields not more than 0.2 percent of residue on ignition.

Chloride, page 784—Shake 750 mg. of Methyclothiazide with 25 ml. of water for 2 minutes, filter through a suitable membrane filter, and add 4 or 5 drops of diluted nitric acid: the acidified filtrate shows no more chloride than corresponds to 0.2 ml. of 0.02 N hydrochloric acid (0.019 percent).

Selenium—A *Test preparation* prepared with 200 mg. of Methyclothiazide meets the requirements of the *Selenium Limit*

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* Patented. See notice, page ii.

Test, page 865 (30 parts per million Se).

Heavy metals, *Method II*, page 806—The heavy metals limit for Methyclothiazide is 20 parts per million.

Diazotizable substances—

Standard preparation—Weigh accurately 10 mg. of NF 4-Amino-6-chloro-N^3-methyl-*m*-benzenedisulfonamide Reference Standard, transfer to a 50-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 25.0 ml. of the resulting solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Each ml. of *Standard preparation* contains 50 mcg. of the reagent.

Test preparation—Weigh accurately 500 mg. of Methyclothiazide, transfer to a 100-ml. volumetric flask, dilute to volume with methanol, and mix.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 50-ml. volumetric flasks. Transfer 2.0 ml. of methanol to a third 50-ml. volumetric flask to serve as a blank. Evaporate the contents of the flasks to dryness on a steam bath, and then dissolve each residue in 0.5 ml. of acetonitrile. To each flask add 2.0 ml. of 0.1 *N* hydrochloric acid and 1.0 ml. of freshly prepared sodium nitrite solution (1 in 1000), and allow to stand for 15 minutes with occasional shaking. Add 2.0 ml. of ammonium sulfamate solution (1 in 50), allow to stand for 5 minutes with frequent swirling, then add 1.0 ml. of *N*-(1-naphthyl)ethylenediamine dihydrochloride solution (1 in 1000) and 10.0 ml. of sodium acetate T.S. Dilute to volume with water, and mix. Concomitantly determine the absorbances of the solutions obtained from the *Standard preparation* and the *Test preparation* in 1-cm. cells at 525 mμ, with a suitable spectrophotometer, using the reagent blank to set the instrument. The absorbance of the solution from the *Test preparation* does not exceed that of the solution from the *Standard preparation*, corresponding to not more than 1 percent of diazotizable substances.

Assay—Transfer about 350 mg. of Methyclothiazide, accurately weighed, to a suitable flask, add 40 ml. of methanolic potassium hydroxide solution (1 in 20), and reflux for 2 hours. Cool, transfer the solution to a tall-form beaker with the aid of about 60 ml. of water, acidify with diluted nitric acid, and titrate with 0.1 *N* silver nitrate, determining the end-point potentiometrically using suitable electrodes. Each ml. of 0.1 *N* silver nitrate is equivalent to 36.02 mg. of $C_9H_{11}Cl_2N_3O_4S_2$.

Packaging and storage—Preserve Methyclothiazide in well-closed containers.

CATEGORY—Diuretic; antihypertensive.

USUAL DOSE RANGE—**2.5** to **10 mg.** once daily, 10 mg. being the maximum single effective dose.

Methyclothiazide Tablets

Methyclothiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{11}Cl_2N_3O_4S_2$.

Identification—The polarogram (see page 847) of the solution employed for measurement in the *Assay* of Methyclothiazide Tablets exhibits a half-wave potential ($E_{1/2}$) within 1 percent of that of NF Methyclothiazide Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Methyclothiazide Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Methyclothiazide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 50-ml. volumetric flask, add about 30 ml. of acetone, and shake mechanically for 1 hour. Dilute to volume with acetone, mix, and centrifuge a portion of the mixture. Evaporate an accurately measured volume of the clear supernatant liquid to dryness with the aid of a current of air, dissolve the residue in methanol, and then dilute quantitatively with methanol to provide a solution containing approximately 10 mcg. of methyclothiazide per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Methyclothiazide Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 267 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_9H_{11}Cl_2N_3O_4S_2$ in the Tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of methyclothiazide, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of methyclothiazide in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Methyclothiazide Tablets.

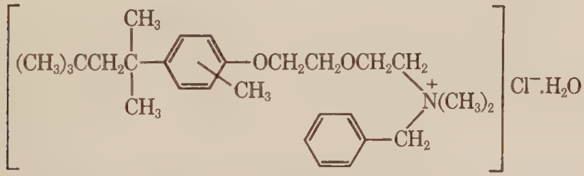
Transfer an accurately weighed portion of the powder, equivalent to about 10 mg. of methyclothiazide, to a 50-ml. volumetric flask. Add 3 ml. of dimethylformamide and about 5 ml. of water, heat on a steam bath for 20 minutes, cool, then add 5 ml. of 1 *M* tetra-*n*-butylammonium chloride and 1 ml. of a 1 in 500 solution of alkyl phenoxy polyethoxy ethanol. Dilute to volume with water, mix, and filter. Transfer a portion of this solution to a polarographic cell. Deaerate by bubbling nitrogen through a gas-washing bottle filled with the diluted solvent (3 ml. of dimethylformamide diluted to 50 ml. with water) and then through the sample solution for 10 to 15 minutes. Insert the dropping mercury electrode of a suitable polarograph, and record the polarogram from −1.35 volts to −1.90 volts, using a mercury pool anode as the reference electrode. Determine the height of the diffusion current $[(i_d)_u]$ as the difference between the residual current and the diffusion current plateau. Concomitantly and similarly determine the diffusion current $[(i_d)_s]$ of a solution containing about 200 mcg. of NF Methyclothiazide Reference Standard in each ml. and the same quantities of the same reagents contained in the sample solution. Calculate the quantity, in mg., of $C_9H_{11}Cl_2N_3O_4S_2$, in the portion of the Tablets taken by the formula $0.05 \times C \times [(i_d)_u/(i_d)_s]$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution.

Packaging and storage—Preserve Methyclothiazide Tablets in well-closed containers.

Tablets available—Methyclothiazide Tablets usually available contain the following amounts of methyclothiazide: 2.5 and 5 mg.

CATEGORY and DOSE—See Methyclothiazide.

Methylbenzethonium Chloride



Benzyldimethyl[2[2[[4-(1,1,3,3-tetramethylbutyl)tolyl]oxy]ethoxy]ethyl]ammonium Chloride

$C_{28}H_{44}ClNO_2 . H_2O$ Mol. wt. 480.14

Methylbenzethonium Chloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{28}H_{44}ClNO_2$, calculated on the dried basis.

Description — Methylbenzethonium Chloride occurs as colorless, hygroscopic crystals, having a very bitter taste and a mild odor. Its solutions are neutral or slightly alkaline to litmus.

Solubility—Methylbenzethonium Chloride is soluble in water, in alcohol, and in chloroform. It is slightly soluble in ether.

Identification—

A: To 1 ml. of a solution of Methylbenzethonium Chloride (1 in 100) add 2 ml. of alcohol, 0.5 ml. of diluted nitric acid, and 1 ml. of silver nitrate T.S.: a white precipitate, which is insoluble in diluted nitric acid and soluble in ammonia T.S., is formed.

B: Treat separate portions of a solution of Methylbenzethonium Chloride (1 in 100) with diluted nitric acid and with mercuric chloride T.S., respectively: precipitates are formed which dissolve upon the addition of alcohol.

C: To 10 ml. of a solution of Methylbenzethonium Chloride (1 in 20,000) add 100 mg. of sodium carbonate, 1 ml. of bromophenol blue T.S. and 10 ml. of benzene, and shake the mixture: the benzene layer is blue.

D: Dissolve 100 mg. of Methylbenzethonium Chloride in 1 ml. of sulfuric acid, add 100 mg. of potassium nitrate, and heat on a steam bath for 3 minutes. Cautiously dilute the solution with water to 10 ml., add 500 mg. of granulated zinc, and warm the mixture for 10 minutes. Cool, add 200 mg. of sodium nitrite to 1 ml. of the clear liquid, and add this mixture to 20 mg. of naphthol sodium disulfonate in 1 ml. of stronger ammonia water: the solution turns orange-red and a brown precipitate may appear.

Melting range, page 814—Methylbenzethonium Chloride, dried at 105° for 4 hours, melts between 161° and 163°.

Loss on drying, page 814—Dry Methylbenzethonium Chloride at 105° for 4 hours:

it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Methylbenzethonium Chloride yields not more than 0.1 percent of residue on ignition.

Ammonia—To 5 ml. of a solution of Methylbenzethonium Chloride (1 in 50) add 3 ml. of sodium hydroxide T.S., and heat to boiling: the odor of ammonia is not perceptible.

Assay—Weigh accurately a quantity of Methylbenzethonium Chloride equivalent to about 500 mg. of dried methylbenzethonium chloride, and transfer, with the aid of 35 ml. of water, to a glass-stoppered, 250-ml. conical separator containing 25 ml. of chloroform. Add 10.0 ml. of freshly prepared potassium iodide solution (1 in 20), stopper the separator, shake well, allow the layers to separate, and discard the chloroform layer. Wash the aqueous layer with three 10-ml. portions of chloroform, and discard the washings. Transfer the aqueous layer to a glass-stoppered, 250-ml. conical flask, and rinse the separator with three 5-ml. portions of water, adding the washings to the flask. Add 40 ml. of cold hydrochloric acid to the flask, mix, and titrate with 0.05 *M* potassium iodate until the solution becomes light brown in color. Add 5 ml. of chloroform, stopper the flask, and shake vigorously. Continue the titration, dropwise, with shaking after each addition, until the chloroform layer becomes colorless and the aqueous layer is clear yellow. Perform a blank determination, using 20 ml. of water as the sample (see *Residual Titrations*, page 883). Each ml. of 0.05 *M* potassium iodate is equivalent to 46.21 mg. of $C_{28}H_{44}ClNO_2$.

Packaging and storage—Preserve Methylbenzethonium Chloride in tight containers.

CATEGORY—Local anti-infective.

FOR EXTERNAL USE—Topically as a 0.055 percent powder.

Methylbenzethonium Chloride Powder

Methylbenzethonium Chloride Powder contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of $C_{28}H_{44}ClNO_2.H_2O$ in a suitable fine powder base, free from grittiness.

Identification—Suspend about 100 mg. of Methylbenzethonium Chloride Powder in 10 ml. of water, add 100 mg. of sodium carbonate, 1 ml. of bromophenol blue T.S., and 10 ml. of benzene, and shake the mixture: the benzene layer is blue.

pH, page 824—The pH of a dispersion of Methylbenzethonium Chloride Powder in carbon dioxide-free water (1 in 100) is between 9.0 and 10.5.

Other tests—Not less than 99 percent of Methylbenzethonium Chloride Powder passes through a No. 200 sieve (see page 849).

Assay—Transfer an accurately weighed portion of Methylbenzethonium Chloride Powder, equivalent to about 500 mcg. of methylbenzethonium chloride, to a glass-stoppered 50-ml. cylinder. Add 5 ml. of chloroform (previously purified by shaking 100 ml. with 10 g. of silica gel, allowing to settle, and withdrawing the supernatant liquid), 5 ml. of phosphoric acid solution (1 in 10), and 1 ml. of safranin O solution (1 in 20,000). Titrate with 0.0001 *N* dioctyl sodium sulfosuccinate until about 1 ml. from the end-point, then shake the stoppered cylinder vigorously for about 2 minutes, and continue the titration in 0.1-ml. increments, shaking vigorously after each addition, until a pink color appears in the chloroform layer. Perform a blank determination and make any necessary correction. Each ml. of 0.0001 *N* dioctyl sodium sulfosuccinate is equivalent to 48.01 mcg. of $C_{28}H_{44}ClNO_2.H_2O$.

Packaging and storage—Preserve Methylbenzethonium Chloride Powder in well-closed containers.

Powder available—Methylbenzethonium Powder usually available contains 0.055 percent of methylbenzethonium chloride.

CATEGORY and USE—See Methylbenzethonium Chloride.

Methyl Isobutyl Ketone

$CH_3CH(CH_3)CH_2COCH_3$

4-Methyl-2-pentanone

$C_6H_{12}O$ Mol. wt. 100.16

Methyl Isobutyl Ketone contains not less than 99.0 percent of $C_6H_{12}O$.

Description—Methyl Isobutyl Ketone is a transparent, colorless, mobile, volatile liquid, having a faint ketonic and camphor odor.

Solubility—Methyl Isobutyl Ketone is slightly soluble in water. It is miscible with alcohol, with ether, and with benzene.

Identification—Transfer 1 ml. of Methyl Isobutyl Ketone to a test tube containing 10 ml. of alcohol. Add water dropwise until the solution is faintly turbid, and remove the turbidity with a few drops of alcohol. Add 1 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate, and shake the mixture vigorously. Immerse the test tube in boiling water for 2 minutes, and cool in an ice bath until crystallization occurs. Collect the precipitate on a filter, wash thoroughly with diluted alcohol, and dry at 105° for 2 hours: the semicarbazone so obtained melts at about 134°, page 814.

Specific gravity, page 866—The specific gravity of Methyl Isobutyl Ketone is not more than 0.799, indicating not less than 99.0 percent of $C_6H_{12}O$.

Distilling range, page 782—Methyl Isobutyl Ketone distils between 114° and 117°.

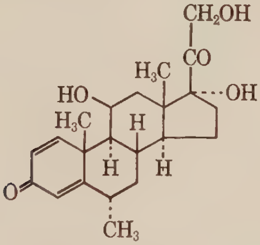
Acidity—Mix 15.0 ml. of Methyl Isobutyl Ketone with 15 ml. of neutralized alcohol, add 3 drops of phenolphthalein T.S., and titrate with 0.05 *N* sodium hydroxide: not more than 0.4 ml. is required for neutralization.

Nonvolatile residue—Evaporate 50 ml. of Methyl Isobutyl Ketone in a tared porcelain dish on a steam bath, and dry at 105° for 1 hour: the weight of the residue does not exceed 4 mg. (80 parts per million w/v).

Packaging and storage—Preserve Methyl Isobutyl Ketone in tight containers.

CATEGORY—Alcohol denaturant.

Methylprednisolone*



11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione

$C_{22}H_{30}O_5$ Mol. wt. 374.48

Methylprednisolone contains not less than 97.0 percent and not more than 103.0 percent of $C_{22}H_{30}O_5$, calculated on the dried basis.

Description—Methylprednisolone occurs as a white to practically white, odorless, crystalline powder. When tested by the method for *Class Ia*, page 815, it melts at about 240° with some decomposition.

Solubility—Methylprednisolone is sparingly soluble in alcohol, in dioxane, and in methanol, slightly soluble in acetone, and in chloroform, and very slightly soluble in ether. It is practically insoluble in water.

Identification—Dissolve about 5 mg. of Methylprednisolone in 2 ml. of sulfuric acid: a red color is produced.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methylprednisolone, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Methylprednisolone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Methylprednisolone in alcohol exhibits maxima and minima at the same wavelengths as that of NF Methylprednisolone Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 243 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Methylprednisolone, calculated on the dried basis, determined in a solution in dioxane containing 100 mg. of Methylprednisolone in each 10 ml., is between +79° and +86°.

Loss on drying, page 814—Dry Methylprednisolone at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Methylprednisolone yields not more than 0.2 percent of residue on ignition.

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* Patented. See notice, page ii.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Methylprednisolone Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Methylprednisolone previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and isopropyl alcohol (4:1), and determining the absorbance at the maximum at about 243 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Methylprednisolone taken: not more than 3 percent is found.

Assay—

Standard preparation—Prepare as directed for *Standard Preparation* under *Steroid Assay*, page 876, using NF Methylprednisolone Reference Standard.

Assay preparation—Weigh accurately about 100 mg. of Methylprednisolone, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Pipet 5.0 ml. of this solution into a 250-ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{22}H_{30}O_5$ in the portion of Methylprednisolone taken by the formula $10C \times (A_U/A_S)$.

Packaging and storage—Preserve Methylprednisolone in tight, light-resistant containers.

CATEGORY—Glucocorticoid.

USUAL DOSE—**4 mg.** four times a day.

USUAL DOSE RANGE—**2** to **60 mg.** daily.

Methylprednisolone Tablets

Methylprednisolone Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $C_{22}H_{30}O_5$.

Identification—Powder a number of Methylprednisolone Tablets, equivalent to about 40 mg. of methylprednisolone, and digest with 25 ml. of solvent hexane for 15 minutes. Filter, and discard the filtrate. Digest the residue with 25 ml. of methanol for 15 minutes. Filter, evaporate the filtrate to dryness, and dry at 105° for 2 hours. The residue so obtained responds to the *Identification test* and meets the requirements for *Infrared absorption* under *Methylprednisolone*, page 449.

Dissolution, *Method I*, page 802—Not less than 50 percent of the labeled amount of $C_{22}H_{30}O_5$ in Methylprednisolone Tablets dissolves into solution within 30 minutes, using a stirring speed of 100 r.p.m. and water as the *Dissolution Fluid*. Determine the amount of $C_{22}H_{30}O_5$ in solution by determining the ultraviolet absorption of filtered aliquots removed from the dissolution solution, at 246 mμ, in 1-cm. cells, with a suitable spectrophotometer, using water as the blank and utilizing a standard curve, representing absorbance *versus* concentration of NF Methylprednisolone Reference Standard.

Content uniformity, *Method I*, page 799—Methylprednisolone Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed for *Standard Preparation* under *Steroid Assay*, page 876, using NF Methylprednisolone Reference Standard.

Assay preparation—Weigh and finely powder not less than 10 Methylprednisolone Tablets. Weigh accurately a portion of the powder, equivalent to about 20 mg. of methylprednisolone, and transfer, with the aid of 15 ml. of water, to a separator. Extract the methylprednisolone completely, using four 25-ml. portions of chloroform, and filtering each portion through chloroform-washed cotton into a 250-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 25.0 ml. of this solution into a 100-ml. volumetric flask, add chloroform to volume, and mix. Pipet 10.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask, evaporate the chloroform on a steam bath just to dryness, cool, and dissolve the residue in 20.0 ml. of alcohol.

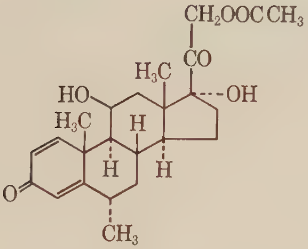
Procedure—Proceed as directed for *Procedure* under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{22}H_{30}O_5$ in the portion of the Tablets taken by the formula $2C \times (A_U/A_S)$.

Packaging and storage—Preserve Methylprednisolone Tablets in tight containers.

Tablets available—Methylprednisolone Tablets usually available contain the following amounts of methylprednisolone: 2, 4, and 16 mg.

CATEGORY and DOSE—See Methylprednisolone.

Methylprednisolone Acetate*



Methylprednisolone 21-Acetate

$C_{24}H_{32}O_6$ Mol. wt. 416.52

Methylprednisolone Acetate contains not less than 97.0 percent and not more than 103.0 percent of $C_{24}H_{32}O_6$, calculated on the dried basis.

Description—Methylprednisolone Acetate occurs as a white or practically white, odorless, crystalline powder. When tested by the method for *Class Ia*, page 815, it melts at about 215° with some decomposition.

Solubility—Methylprednisolone Acetate is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol and slightly soluble in ether. It is practically insoluble in water.

Identification—

A: Dissolve about 5 mg. of Methylprednisolone Acetate in 2 ml. of sulfuric acid: a wine-red color is produced.

B: Place about 5 mg. of Methylprednisolone Acetate in a test tube, add 2 ml. of alcoholic potassium hydroxide T.S., and heat in a boiling water bath for 5 minutes. Cool, add 2 ml. of dilute sulfuric acid (1 in 3.5), and boil gently for about 1 minute: the odor of ethyl acetate is perceptible.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methylprednisolone Acetate, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Methylprednisolone Acetate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Methylprednisolone Acetate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Methylprednisolone Acetate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 243 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Methylprednisolone Acetate, calculated on the dried basis, determined in a solution in dioxane containing 100 mg. of Methylprednisolone Acetate in each 10 ml., is between +97° and +105°.

Loss on drying, page 814—Dry Methylprednisolone Acetate at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Methylprednisolone Acetate yields not more than 0.2 percent of residue on ignition.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Methylprednisolone Acetate Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Methylprednisolone Acetate previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and isopropyl alcohol (4:1), and determining the absorbance at the maximum at about 243 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Methylprednisolone Acetate taken: not more than 3 percent is found.

Assay—

Standard preparation—Prepare as directed for *Standard Preparation* under *Steroid Assay*, page 876, using NF Methylprednisolone Acetate Reference Standard.

Assay preparation—Weigh accurately about 100 mg. of Methylprednisolone Acetate, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Pipet 5.0 ml. of this solution into a 250-ml. volumetric flask, add alcohol to volume, and mix.

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* Patented. See notice, page ii.

Pipet 20.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay,* page 876. Calculate the quantity, in mg., of $C_{24}H_{32}O_6$ in the portion of Methylprednisolone Acetate taken by the formula $10C \times (A_U/A_S)$.

Packaging and storage—Preserve Methylprednisolone Acetate in tight, light-resistant containers.

CATEGORY—Glucocorticoid.

USUAL DOSE—Intra-articular or intramuscular, **40 mg.**

USUAL DOSE RANGE—**10** to **80 mg.**

Sterile Methylprednisolone Acetate Suspension

Sterile Methylprednisolone Acetate Suspension is a sterile suspension of methylprednisolone acetate in a suitable aqueous medium. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{24}H_{32}O_6$.

Identification—Filter a volume of Sterile Methylprednisolone Acetate Suspension, equivalent to about 100 mg. of methylprednisolone acetate, through paper. Wash the residue with several 5-ml. portions of water, and dry at 105° for 3 hours: the methylprednisolone acetate so obtained responds to the *Identification tests* and meets the requirements for *Infrared absorption* under *Methylprednisolone Acetate,* page 451.

pH, page 824—The pH of Sterile Methylprednisolone Acetate Suspension is between 3.5 and 7.0.

Other requirements—Sterile Methylprednisolone Acetate Suspension meets the requirements under *Injections,* page 810.

Particle size—Transfer 1 drop of Sterile Methylprednisolone Acetate Suspension to a microscope slide and spread evenly, diluting with water, if necessary, to decrease the density of the field. Examine the slide under a microscope, equipped with a calibrated ocular micrometer, using about 400× magnification. Scan the entire slide, and note the size of the individual particles: not less than 99 percent of the particles are less than 20 μ in length when measured along the longest axis, and not less than 75 percent of the particles are less than 10 μ.

Assay—

Standard preparation—Proceed as directed for *Standard Preparation* under *Steroid Assay,* page 876, using NF Methylprednisolone Acetate Reference Standard.

Assay preparation—Transfer to a separator an accurately measured volume of Sterile Methylprednisolone Acetate Suspension, equivalent to about 40 mg. of methylprednisolone acetate, and add 10 ml. of water. Extract the methylprednisolone acetate completely, using four 25-ml. portions of chloroform, filtering each portion through chloroform-washed cotton into a 200-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 10.0 ml. of this solution into a 100-ml. volumetric flask, add chloroform to volume, and mix. Pipet 10.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask, evaporate the chloroform on a steam bath just to dryness, cool, and dissolve the residue in 20.0 ml. of alcohol.

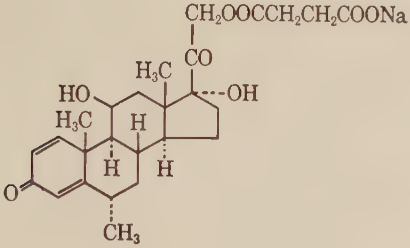
Procedure—Proceed as directed for *Procedure* under *Steroid Assay,* page 876. Calculate the quantity, in mg., of $C_{24}H_{32}O_6$ in the volume of the Suspension taken by the formula $4C \times (A_U/A_S)$.

Packaging and storage—Preserve Sterile Methylprednisolone Acetate Suspension in single-dose or multiple-dose containers, preferably of Type I glass.

Suspensions available—Sterile Methylprednisolone Acetate Suspension usually available contains the following amounts of methylprednisolone acetate: 40 mg. in 1 ml. and 100 and 200 mg. in 5 ml.

CATEGORY and DOSE—See Methylprednisolone Acetate.

Methylprednisolone Sodium Succinate*



Methylprednisolone 21-(Hydrogen Succinate) Sodium Salt

$C_{26}H_{33}NaO_8$ Mol. wt. 496.54

Methylprednisolone Sodium Succinate contains not less than 97.0 percent and not more than 103.0 percent of $C_{26}H_{33}NaO_8$, calculated on the dried basis.

Description—Methylprednisolone Sodium Succinate occurs as a white, or nearly white, odorless, hygroscopic, amorphous solid.

Solubility—Methylprednisolone Sodium Succinate is very soluble in water and in alcohol. It is insoluble in chloroform, and is very slightly soluble in acetone.

Identification—

A: Dissolve about 100 mg. of Methylprednisolone Sodium Succinate in 5 ml. of water, and add 0.5 ml. of hydrochloric acid: a white precipitate is formed immediately.

B: Dissolve about 3 mg. of Methylprednisolone Sodium Succinate in 2 ml. of sulfuric acid, and allow to stand for 5 minutes: a wine-red color, free from fluorescence, is produced.

C: Methylprednisolone Sodium Succinate responds to the flame test for *Sodium*, page 810.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methylprednisolone Sodium Succinate, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Methylprednisolone Sodium Succinate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Methylprednisolone Sodium Succinate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Methylprednisolone Sodium Succinate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 243 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Methylprednisolone Sodium Succinate, calculated on the dried basis, determined in a solution in alcohol containing 100 mg. of Methylprednisolone Sodium Succinate in each 10 ml., is between +96° and +104°.

Loss on drying, page 814—Dry Methylprednisolone Sodium Succinate at 105° for 3 hours: it loses not more than 3 percent of its weight.

Sodium content—Dissolve, with gentle heating, about 1 g. of Methylprednisolone Sodium Succinate, accurately weighed, in 75 ml. of glacial acetic acid. Add 20 ml. of dioxane, then add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 2.299 mg. of Na. Not less than 4.49 percent and not more than 4.77 percent is found, calculated on the dried basis.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Methylprednisolone Sodium Succinate Reference Standard dissolved in alcohol instead of chloroform-alcohol.

Test preparation—Weigh accurately about 80 mg. of Methylprednisolone Sodium Succinate previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of alcohol to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and isopropyl alcohol (4:1), and determining the absorbance at the maximum at about 243 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Methylprednisolone Sodium Succinate taken: not more than 3 percent is found.

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* Patented. See notice, page ii.

Assay—

Standard preparation—Proceed as directed under *Steroid Assay*, page 876, using NF Methylprednisolone Sodium Succinate Reference Standard, except dilute to a solution containing about 12.5 mcg. per ml.

Assay preparation—Weigh accurately about 100 mg. of Methylprednisolone Sodium Succinate, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Pipet 5.0 ml. of this solution into a 200-ml. volumetric flask, add alcohol to volume, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask.

Procedure—To each of the flasks containing the *Assay preparation* and the *Standard preparation*, and a similar flask containing 20.0 ml. of alcohol, to serve as the blank, add 2.0 ml. of blue tetrazolium T.S., mix, then to each flask add 4.0 ml. of dilute (1 in 10 with alcohol) tetramethylammonium hydroxide T.S. Mix, allow to stand in the dark for 90 minutes, add 1.0 ml. of glacial acetic acid, mix, and complete as directed under *Steroid Assay*, page 876, beginning with "... and concomitantly determine the absorbances...." Calculate the quantity, in mg., of $C_{26}H_{33}NaO_8$ in the portion of Methylprednisolone Sodium Succinate taken by the formula $8C \times (A_U/A_S)$.

Packaging and storage—Preserve Methylprednisolone Sodium Succinate in tight, light-resistant containers.

Category—Glucocorticoid.

Usual dose—Intravenous or intramuscular, the equivalent of **40 mg.** of methylprednisolone every 6 to 24 hours.

Usual dose range—The equivalent of **10 to 125 mg.** of methylprednisolone.

Methylprednisolone Sodium Succinate for Injection

Methylprednisolone Sodium Succinate for Injection is sterile methylprednisolone sodium succinate with suitable buffers. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{30}O_5$ (methylprednisolone) in each single compartment container, or in the volume of reconstituted injection designated on the label, when the container is constructed to hold separately the Methylprednisolone Sodium Succinate for Injection and the solution for reconstitution.

Identification—Transfer about 100 mg. of Methylprednisolone Sodium Succinate for Injection to a glass-stoppered flask, add 20 ml. of methanol, shake for 5 minutes, and filter. Evaporate the filtrate to dryness on a steam bath, dry at 60° in vacuum for 3 hours, and place in a desiccator until the residue crystallizes: the residue so obtained responds to *Identification test B* and meets the requirements for *Infrared absorption* under *Methylprednisolone Sodium Succinate*, page 453.

Content uniformity, *Method I*, page 798—Methylprednisolone Sodium Succinate for Injection meets the requirements of the content uniformity test for sterile solids.

pH, page 824—The pH of a solution of Methylprednisolone Sodium Succinate for Injection containing about 50 mg. of methylprednisolone sodium succinate in each ml. is between 7.0 and 8.0.

Loss on drying, page 814—Dry Methylprednisolone Sodium Succinate for Injection at 105° for 3 hours: it loses not more than 2 percent of its weight.

Other requirements—Methylprednisolone Sodium Succinate for Injection meets the requirements for *Sterility Tests*, page 874, and *Labeling* under *Injections*, page 810.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using NF Methylprednisolone Sodium Succinate Reference Standard, except dilute to a solution containing about 12.5 mcg. per ml.

Assay preparation—Transfer an accurately weighed portion of Methylprednisolone Sodium Succinate for Injection or an accurately measured volume of the reconstituted Injection, equivalent to about 50 mg. of methylprednisolone, to a 100-ml. volumetric flask, add water to volume, and mix. Pipet 10.0 ml. of this solution into a separator, and add 10 ml. of water and 5 ml. of diluted hydrochloric acid. Extract the steroid completely, using four 25-ml. portions of chloroform, filtering each extract through chloroform-washed cotton into a 250-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 10.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask, evaporate the chloroform just to dryness on a steam bath, and dissolve the residue in 20.0 ml. of alcohol.

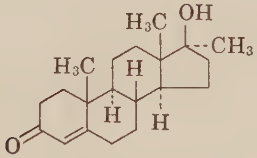
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Methylprednisolone Sodium Succinate*, page 453. Calculate the quantity, in mg., of $C_{22}H_{30}O_5$ in the portion of the sample taken by the formula $5C \times 0.7542 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Methylprednisolone Sodium Succinate Reference Standard in the *Standard preparation*, and 0.7542 is the ratio of the molecular weight of methylprednisolone to methylprednisolone sodium succinate.

Packaging and storage—Preserve Methylprednisolone Sodium Succinate for Injection in *Containers for Sterile Solids* as described under *Injections*, page 810.

Sizes available—Methylprednisolone Sodium Succinate for Injection usually available contains an amount of methylprednisolone sodium succinate equivalent to the following amounts of methylprednisolone: 40 mg. and 125 mg.

CATEGORY and DOSE—See Methylprednisolone Sodium Succinate.

Methyltestosterone



17β-Hydroxy-17-methylandrost-4-en-3-one

$C_{20}H_{30}O_2$ Mol. wt. 302.46

Methyltestosterone contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{30}O_2$, calculated on the dried basis.

Description—Methyltestosterone occurs as white or creamy white crystals or crystalline powder. It is odorless and is stable in air, but is slightly hygroscopic. It is affected by light.

Solubility—Methyltestosterone is insoluble in water. It is practically insoluble in alcohol, in methanol, in ether, and in other organic solvents, and sparingly soluble in vegetable oils.

Melting range, *Class Ia*, page 815—Methyltestosterone melts between 163° and 168°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methyltestosterone, previously dried in vacuum over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Methyltestosterone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Methyltestosterone in alcohol exhibits maxima and minima at the same wavelengths as that of NF Methyltestosterone Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Methyltestosterone, previously dried in vacuum over silica gel for 4 hours, determined in a solution in benzene containing 100 mg. of Methyltestosterone in 10 ml., is between +84° and +87°.

Loss on drying, page 814—Dry Methyltestosterone in vacuum over silica gel for 4 hours: it loses not more than 1 percent of its weight.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Methyltestosterone Reference Standard to prepare a solution containing approximately 4 mg. per ml.

Test preparation—Weigh accurately about 40 mg. of Methyltestosterone, previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and ethyl acetate (1:1), and determining the absorbance at the maximum at about 241 mμ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Methyltestosterone taken: not more than 3 percent is found.

Assay—Transfer to a 200-ml. volumetric flask about 100 mg. of Methyltestosterone, accurately weighed, add alcohol to volume, and mix. Transfer 10.0 ml. of the solution to a 500-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methyltestosterone Reference Standard in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity of $C_{20}H_{30}O_2$ in the Methyltestosterone taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Methyltestosterone in well-closed, light-resistant containers.

Category—Androgen.

Usual dose—Oral, **10 mg.** three times a day; buccal, **5 mg.** up to four times a day.

Usual dose range—Oral, **10** to **50 mg.** per day; buccal **5** to **25 mg.** per day.

Methyltestosterone Tablets

Methyltestosterone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{30}O_2$.

Identification—Evaporate to dryness 25 ml. of the first alcohol solution of methyltestosterone obtained in the *Assay* of Methyltestosterone Tablets: the infrared absorption spectrum of a potassium bromide dispersion of the residue exhibits maxima at the same wavelengths as that of NF Methyltestosterone Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Methyltestosterone Tablets is 30 minutes. Methyltestosterone Tablets intended for buccal administration meet the requirements set forth for *Buccal tablets,* page 837.

Content uniformity, *Method II,* page 799—Methyltestosterone Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask, add 50 ml. of methanol, and shake mechanically for 60 minutes. Dilute to volume with methanol, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol to provide a solution containing approximately 10 mcg. of methyltestosterone per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Methyltestosterone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{20}H_{30}O_2$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of methyltestosterone in the tablet; D is the exact concentration, in mcg. per ml., of methyltestosterone in the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Methyltestosterone Tablets. Weigh accurately a portion of the powder, equivalent to about 10 mg. of methyltestosterone, and transfer to a 125-ml. separator with the aid of about 5 ml. of water. Extract with four 25-ml. portions of chloroform, filtering each through chloroform-washed cotton. Evaporate the combined extracts on a steam bath, with the aid of a current of air, to dryness. Dissolve the residue in alcohol, transfer to a 50-ml. volumetric flask, and add alcohol to volume, and mix. Pipet a 5.0-ml. aliquot into a 100-ml. volumetric flask, add alcohol to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Methyltestosterone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml. in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{20}H_{30}O_2$ in the portion of the Tablets taken, by the formula $C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

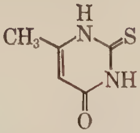
Packaging and storage—Preserve Methyltestosterone Tablets in well-closed containers.

Tablets available—Methyltestosterone

Tablets usually available contain the following amounts of methyltestosterone: 5, 10, and 25 mg.

Category and Dose—See Methyltestosterone.

Methylthiouracil



6-Methyl-2-thiouracil

$C_5H_6N_2OS$

Mol. wt. 142.18

Methylthiouracil contains not less than 97.0 percent and not more than 100.5 percent of $C_5H_6N_2OS$, calculated on the dried basis.

Description—Methylthiouracil occurs as a white, odorless, crystalline powder. It melts with decomposition at about 330°.

Solubility—Methylthiouracil is very slightly soluble in water, sparingly soluble in alcohol, and slightly soluble in chloroform and in ether. It is freely soluble in ammonia and in solutions of alkali hydroxides.

Identification—

A: Dissolve about 10 mg. of Methylthiouracil in a mixture of 4 ml. of sodium hydroxide T.S. and 6 ml. of water. To 2 ml. of the solution add 3 drops of sodium nitroferricyanide T.S., shake for a few seconds, then add 2 ml. of acetic acid: a blue color is produced.

B: To about 25 mg. of Methylthiouracil in a test tube slowly add bromine T.S. until solution is complete, then gently boil the solution until the excess bromine is expelled. Cool, and add 10 ml. of barium hydroxide T.S.: a white precipitate is formed (with *thiouracil* the white precipitate first formed turns violet in about 1 minute).

Loss on drying, page 814—Dry Methylthiouracil at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 200 mg. of Methylthiouracil is negligible. Retain the residue for the *Heavy metals test.*

Sulfate—Heat 100 mg. of Methylthiouracil with 10 ml. of water and 5 drops of diluted hydrochloric acid on a steam bath for 10 minutes, filter, and add to the filtrate 1 ml. of barium chloride T.S.: no turbidity is produced in 1 minute.

Selenium—A *Test Preparation* prepared with 200 mg. of Methylthiouracil meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Heavy metals, page 806—To the residue obtained in the test for *Residue on ignition* add 3 drops of hydrochloric acid and 2 drops of nitric acid, and evaporate on a steam bath to dryness. Add 10 ml. of hot water, digest for 2 minutes, filter, wash with about 10 ml. of water, then add 2 ml. of diluted acetic acid, and dilute to 25 ml.: the heavy metals limit for Methylthiouracil is 20 parts per million.

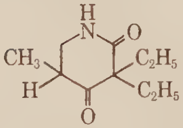
Sulfur—Weigh accurately about 50 mg. of Methylthiouracil, and proceed as directed under *Oxygen Flask Combustion,* page 823, beginning with "Place the sample, together with a filter paper fuse-strip . . . .," and using a mixture of 5 ml. of water and 2.5 ml. of hydrogen peroxide T.S. as the absorbing liquid. Following combustion, fill the cup of the flask with water, loosen the stopper, and then rinse the stopper, sample holder, and sides of the flask with water. Remove the stopper, heat the contents of the flask to boiling, and boil for about 2 minutes. Cool, add 3 drops of phenolphthalein T.S., and titrate with 0.05 *N* sodium hydroxide. Each ml. of 0.05 *N* sodium hydroxide is equivalent to 801.6 mcg. of sulfur. The amount of sulfur found, calculated on the dried basis, is not less than 22.2 percent and not more than 22.8 percent.

Assay—Dissolve about 300 mg. of Methylthiouracil, accurately weighed, in 80 ml. of dimethylformamide. Add 5 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate with 0.1 *N* sodium methoxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium methoxide is equivalent to 14.22 mg. of $C_5H_6N_2OS$.

Packaging and storage—Preserve Methylthiouracil in well-closed, light-resistant containers.

Category—Thyroid suppressant.
Usual dose—**50 mg.** four times a day.

Methyprylon*



3,3-Diethyl-5-methyl-2,4-piperidinedione

$C_{10}H_{17}NO_2$ Mol. wt. 183.25

Methyprylon contains not less than 98.0 percent and not more than 101.0 percent of $C_{10}H_{17}NO_2$, calculated on the dried basis.

Description—Methyprylon occurs as a white, or nearly white, crystalline powder. It has a slight characteristic odor.

Solubility—Methyprylon is soluble in water, and is very soluble in alcohol, in chloroform, in ether, and in benzene.

Identification—Add 50 mg. of Methyprylon to a mixture of 5 ml. of water and 2 ml. of sodium hydroxide T.S., mix, and add 0.5 ml. of potassium ferricyanide T.S.: the solution shows a green fluoroescence under ultraviolet light.

Melting range, page 814—Methyprylon melts between 75° and 78.5°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methyprylon, previously dried at 56° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Methyprylon Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 333 solution of Methyprylon in isopropyl alcohol exhibits maxima and minima at the same wavelengths as that of NF Methyprylon Reference Standard, similarly measured. The absorptivity at the maximum occurring at about 295 mμ is not more than 0.25.

Loss on drying, page 814—Dry Methyprylon in vacuum at 56° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Methyprylon yields not more than 0.1 percent of residue on ignition.

Assay—

Potassium ferricyanide, 0.1 N—Transfer about 33 g. of potassium ferricyanide, accurately weighed, and 12.4 g. of monohydrated sodium carbonate into a 1-liter volumetric flask. Dissolve the two salts in sufficient water to make 1.0 liter. Determine the normality of the solution as directed in the *Procedure* using NF Methyprylon Reference Standard as the primary standard. Store the solution in amber-colored bottles, and standardize just before use.

Procedure—Transfer about 250 mg. of Methyprylon, accurately weighed, into a 150-ml. beaker and add 60 ml. of water and 10 ml. of potassium hydroxide T.S. Calculate the expected end-point, and titrate potentiometrically, using a calomel-platinum electrode system. Add the *0.1 N potassium ferricyanide*, rapidly at first, to within about 3 ml. of the calculated end-point and then in 0.2-ml. increments until the final deflection of the instrument. Each ml. of *0.1 N potassium ferricyanide* is equivalent to 9.162 mg. of $C_{10}H_{17}NO_2$.

Packaging and storage—Preserve Methyprylon in well-closed, light-resistant containers.

CATEGORY—Sedative.

USUAL DOSE RANGE—**50** to **400 mg.** at bedtime.

Methyprylon Capsules

Methyprylon Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{10}H_{17}NO_2$.

Identification—Extract the contents of a Methyprylon Capsule, equivalent to about 300 mg. of methyprylon, with 10 ml. of ether, filter the extract into a beaker, and evaporate to dryness on a steam bath: a 50-mg. portion of the residue responds to the *Identification test* under *Methyprylon*, page 458.

Weight variation, page 901—Methyprylon Capsules meet the requirements of the weight variation test for capsules.

Assay—

Potassium ferricyanide, 0.1 N—Prepare and standardize as directed in the *Assay* under *Methyprylon*, page 458.

Procedure—Transfer as completely as

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* Patented. See notice, page ii.

possible the contents of not less than 20 Methyprylon Capsules to a suitable tared container, and determine the average weight per capsule. Mix the combined contents thoroughly, and transfer an accurately weighed portion, equivalent to about 250 mg. of methyprylon, to a 150-ml. beaker. Add 70 ml. of water and 10 ml. of potassium hydroxide T.S., and continue as directed for *Procedure* in the *Assay* under *Methyprylon*, page 458, beginning with "Calculate the expected end-point. . . ."

Packaging and storage—Preserve Methyprylon Capsules in tight, light-resistant containers.

Capsules available—Methyprylon Capsules usually available contain the following amount of methyprylon: 300 mg.

CATEGORY AND DOSE—See Methyprylon.

Methyprylon Tablets

Methyprylon Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{17}NO_2$.

Identification—Extract a quantity of finely powdered Methyprylon Tablets, equivalent to about 200 mg. of methyprylon, with 10 ml. of ether. Filter the ether extract into a beaker, and evaporate to dryness on a steam bath: a 50-mg. portion of the residue responds to the *Identification test* under *Methyprylon*, page 458.

Disintegration, page 878—The disintegration time limit for Methyprylon Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Methyprylon Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Potassium ferricyanide, 0.1 N—Prepare and standardize as directed in the *Assay* under *Methyprylon*, page 458.

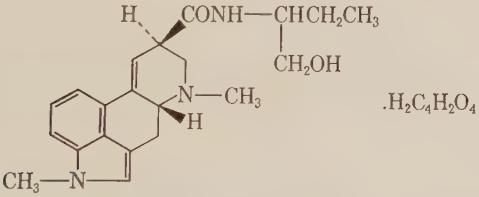
Procedure—Weigh and finely powder not less than 20 Methyprylon Tablets. Weigh accurately a portion of the powder, equivalent to about 250 mg. of methyprylon, and transfer it to a 150-ml. beaker. Add 70 ml. of water and 10 ml. of potassium hydroxide T.S., and continue as directed for *Procedure* in the *Assay* under *Methyprylon*, page 458, beginning with "Calculate the expected end-point. . . ."

Packaging and storage—Preserve Methyprylon Tablets in tight, light-resistant containers.

Tablets available—Methyprylon Tablets usually available contain the following amounts of methyprylon: 50 and 200 mg.

CATEGORY AND DOSE—See Methyprylon.

Methysergide Maleate*



(+)-9,10-Didehydro-*N*-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8β-carboxamide Maleate (1:1)

$C_{21}H_{27}N_3O_2 . C_4H_4O_4$ Mol. wt. 469.54

Methysergide Maleate contains not less than 97.0 percent and not more than 103.0 percent of $C_{21}H_{27}N_3O_2 . C_4H_4O_4$, calculated on the dried basis.

Description—Methysergide Maleate occurs as a white to yellowish white, crystalline powder. It is odorless or has not more than a slight odor.

Solubility—Methysergide Maleate is slightly soluble in water and in alcohol. It is very slightly soluble in chloroform, and is practically insoluble in ether.

Identification—

A: Dissolve about 1 mg. of Methysergide Maleate in 1 ml. of alcohol, and add 2 ml. of *p*-dimethylaminobenzaldehyde T.S.: a violet-blue color develops.

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* Patented. See notice, page ii.

B: [Note: Conduct this test without exposure to daylight, and with the minimum necessary exposure to artificial light.] Prepare a solution of Methysergide Maleate in methanol containing 5 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 25 µl. of this solution and 25 µl. of a methanol solution of NF Methysergide Maleate Reference Standard containing 5 mg. per ml. Wet the spots with 1 *N* sodium bicarbonate from a micropipet, and develop the chromatogram in a solvent system consisting of chloroform and methanol (10:1) until the solvent front has ascended for a distance of about 10 cm. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with a solution prepared by dissolving 800 mg. of *p*-dimethylaminobenzaldehyde in a cooled mixture of 80 ml. of alcohol and 20 ml. of sulfuric acid; allow the plate to dry, and then expose it briefly to fumes of a mixture of nitric and hydrochloric acids. The R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Methysergide Maleate, previously dried in vacuum at 120° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Methysergide Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Methysergide Maleate in tartaric acid solution (1 in 100) exhibits maxima and minima at the same wavelengths as that of NF Methysergide Maleate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 322 mµ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Methysergide Maleate, calculated on the dried basis, determined in a solution in water containing 25 mg. of Methysergide Maleate in each 10 ml., is between +35° and +45°.

Loss on drying, page 814—Dry Methysergide Maleate in vacuum at 120° for 2 hours: it loses not more than 7 percent of its weight.

Assay—Dissolve about 200 mg. of Methysergide Maleate, accurately weighed, in 30 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 46.95 mg. of $C_{21}H_{27}N_3O_2 . C_4H_4O_4$.

Packaging and storage—Preserve Methysergide Maleate in tight, light-resistant containers, in a cold place.

Category—Antiadrenergic (migraine prophylactic).

Usual dose—**4 mg.** to **8 mg.** daily in divided doses, preferably with meals.

Methysergide Maleate Tablets

Methysergide Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{27}N_3O_2 . C_4H_4O_4$.

Identification—To 5 ml. of the *Assay preparation* prepared as directed in the *Assay* add 10 ml. of *p*-dimethylaminobenzaldehyde T.S.: a violet-blue color develops.

Disintegration, page 878—The disintegration time limit for Methysergide Maleate Tablets, using simulated gastric fluid T.S. as the test medium in place of water, is 20 minutes.

Content uniformity, *Method I*, page 799—Methysergide Maleate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Transfer about 20 mg. of NF Methysergide Maleate Reference Standard, previously dried at 120° in vacuum for 2 hours and accurately weighed, to a 100-ml. volumetric flask, add tartaric acid solution (1 in 100) to volume, and mix.

Assay preparation—Weigh and finely powder not less than 20 Methysergide Maleate Tablets. Weigh accurately a portion of powder, equivalent to about 20 mg. of methysergide maleate, and transfer it to a 100-ml. volumetric flask. Add 50 ml. of tartaric acid solution (1 in 100) and 4 drops of benzalkonium chloride solution (1 in 10), and shake vigorously on a mechanical shaker for 30 minutes. Dilute to volume with the tartaric acid solution, mix, and filter, discarding the first 20 ml.

of filtrate. Use the subsequent filtrate as directed in the *Procedure*.

Procedure—Transfer 15.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 50-ml. volumetric flasks, and dilute to volume with tartaric acid solution (1 in 100). Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 322 mμ, with a suitable spectrophotometer, using the tartaric acid solution as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{27}N_3O_2.C_4H_4O_4$ in the portion of the Tablets taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Methysergide Maleate Tablets in tight containers.

Tablets available—Methysergide Maleate Tablets usually available contain the following amount of methysergide maleate: 2 mg.

Category and Dose—See Methysergide Maleate.

Microcrystalline Cellulose, page 143
Mild Silver Protein, page 633
Milk of Bismuth, page 101

Mineral Oil Emulsion

Mineral Oil	**500 ml.**
Acacia, in very fine powder	**125 g.**
Syrup	**100 ml.**
Vanillin	**40 mg.**
Alcohol	**60 ml.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Mix the mineral oil with the powdered acacia in a dry mortar, add 250 ml. of purified water all at once, and emulsify the mixture. Then add, in divided portions, triturating after each addition, a mixture of the syrup, 50 ml. of purified water, and the vanillin dissolved in the alcohol. Finally add sufficient purified water to make the product measure 1000 ml., and mix well.

The vanillin may be replaced by not more than 1 percent of any other official flavoring substance or any mixture of official flavoring substances. Sixty ml. of sweet orange peel tincture, or 2 g. of benzoic acid may be used as a preservative in place of the alcohol.

For other permissible modifications, see *Emulsions*, page 827.

Alcohol content, page 772 (when present)—Mineral Oil Emulsion contains from 4 to 6 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Mineral Oil Emulsion in tight containers.

Category—Cathartic.
Usual dose—**30 ml.**

Light Mineral Oil

Light Mineral Oil is a mixture of liquid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

Description—Light Mineral Oil is a colorless, transparent, oily liquid, free, or nearly free, from fluorescence. It is odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated.

Solubility—Light Mineral Oil is insoluble in water and in alcohol. It is miscible with most fixed oils, but not with castor oil. It is soluble in volatile oils.

Specific gravity, page 866—The specific gravity of Light Mineral Oil is not less than 0.818 and not more than 0.880.

Viscosity, page 889—Light Mineral Oil has a kinematic viscosity of not more than 37 centistokes at 37.8°.

Reaction—Boil 10 ml. of Light Mineral Oil with an equal volume of alcohol: the alcohol remains neutral to moistened litmus.

Readily carbonizable substances, page 856—Place 5 ml. of Light Mineral Oil in a glass-stoppered test tube which has been previously rinsed with chromic acid cleansing mixture, then rinsed with water, and dried. Add 5 ml. of sulfuric acid containing from 94.5 percent to 94.9 percent of H_2SO_4, and heat in a boiling water bath for 10 minutes. After the test tube has been in the bath for 30 seconds, remove it quickly, hold with the finger over the stopper, and give three vigorous, vertical shakes over an amplitude of about 12 cm. Repeat every 30 seconds. Do not keep the test tube out of the bath longer than 3 seconds for each shaking period. At the end of 10 minutes from the time when first placed in the water bath, remove the test tube: the Light Mineral Oil remains unchanged in color and the acid has no more color than the standard color produced by mixing in a similar test tube 3 ml. of ferric chloride C.S., 1.5 ml. of cobaltous chloride C.S., and 0.5 ml. of cupric sulfate C.S., this mixture being overlaid with 5 ml. of Light Mineral Oil.

Solid paraffin—Fill a tall, cylindrical, standard oil-sample bottle of colorless glass of about 120-ml. capacity with Light Mineral Oil, which has been dried previously in a beaker at 105° for 2 hours and cooled to room temperature in a desiccator over phosphorus pentoxide. Stopper, and immerse the bottle in a mixture of ice and water for 4 hours: the Light Mineral Oil is sufficiently clear that a black line 0.5 mm. in width, on a white background, held vertically behind the sample bottle, is easily seen.

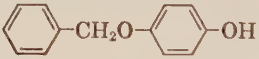
Sulfur compounds—Prepare a saturated solution of lead monoxide in a solution of sodium hydroxide (1 in 5), and mix 2 drops of the clear solution with 4 ml. of Light Mineral Oil and 2 ml. of dehydrated alcohol: the mixture does not darken after heating at 70° for 10 minutes and cooling.

Packaging and storage—Preserve Light Mineral Oil in tight containers.

CATEGORY—Vehicle.

Monobasic Potassium Phosphate, page 576

Monobenzone



p-(Benzyloxy)phenol

$C_{13}H_{12}O_2$ Mol. wt. 200.24

Monobenzone, dried at 105° for 3 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{13}H_{12}O_2$.

Description—Monobenzone occurs as a white, odorless, crystalline powder.

Solubility—Monobenzone is freely soluble in alcohol and in acetone. It is practically insoluble in water.

Identification—The acetate of Monobenzone obtained in the *Assay* melts between 114° and 116°, page 814.

Melting range, page 814—Monobenzone melts between 115° and 118°.

Loss on drying, page 814—Dry Monobenzone at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Monobenzone yields not more than 0.5 percent of residue on ignition.

Assay—Transfer about 400 mg. of Monobenzone, previously dried at 105° for 3 hours and accurately weighed, to a 100-ml. flask fitted with a reflux condenser. Add 5 ml. of pyridine and 3 ml. of acetic anhydride, reflux for 10 minutes, and cool. Transfer the contents of the flask to a 250-ml. beaker containing 100 ml. of water, and rinse the flask with two 3-ml. portions of acetone, collecting the rinsings in the beaker. Cool the contents of the beaker in a refrigerator for 1 hour, collect the precipitate in a tared sintered-glass crucible, and wash the precipitate with water until no odor of pyridine remains. Dry the precipitate overnight in a vacuum desiccator over phosphorus pentoxide: the weight of the monobenzone acetate so obtained, multiplied by 0.8265, represents its equivalent of $C_{13}H_{12}O_2$.

Packaging and storage—Preserve Monobenzone in well-closed containers.

CATEGORY—Depigmenting agent.

FOR EXTERNAL USE—Topically as a 20 percent ointment or 5 percent lotion one or two times daily.

Monobenzone Lotion

Monobenzone Lotion is a solution of monobenzone in isopropyl alcohol and propylene glycol. It contains not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{13}H_{12}O_2$.

Solubility—Monobenzone Lotion is miscible with ethyl alcohol and with isopropyl alcohol. It is not miscible with water.

Identification—The acetate of monobenzone obtained in the *Assay* melts between 114° and 116°, page 814.

Assay—Transfer an accurately measured volume of Monobenzone Lotion, equivalent to about 500 mg. of monobenzone, to a 250-ml. beaker, heat on a steam bath in a current of air to remove the volatile solvent, and cool. Add 100 ml. of water, mix by stirring, and cool in a refrigerator for 1 hour. Centrifuge the mixture, decant the supernatant liquid, wash the monobenzone with water, again centrifuge, and decant the water. Transfer the monobenzone to a separator, with the aid of water, and adjust the volume to about 100 ml. Extract with four 25-ml. portions of chloroform, filtering the extracts through a pledget of cotton into a 150-ml. flask. Evaporate the chloroform in a current of warm air, and add 5 ml. of pyridine and 3 ml. of acetic anhydride to the dry residue. Connect the flask to a reflux condenser, reflux for 10 minutes, cool, and proceed as directed in the *Assay* under *Monobenzone*, page 462, beginning with "Transfer the contents of the flask . . . ."

Packaging and storage—Preserve Monobenzone Lotion in tight, light-resistant containers.

Lotion available—Monobenzone Lotion usually available contains 5 percent monobenzone.

Category—See Monobenzone.

Monobenzone Ointment

Monobenzone Ointment contains not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{13}H_{12}O_2$.

Solubility—Monobenzone Ointment is miscible with, but not soluble in, water.

Identification—The acetate of monobenzone obtained in the *Assay* melts between 114° and 116°, page 814.

Assay—Transfer an accurately weighed amount of Monobenzone Ointment, equivalent to about 500 mg. of monobenzone, to a centrifuge bottle, add 100 ml. of water, and shake until the ointment is completely dispersed. Centrifuge the suspension, decant the supernatant liquid, wash the monobenzone with water, again centrifuge, and decant the water. Transfer the monobenzone to a separator, with the aid of water, and adjust the volume to about 100 ml. Extract with four 25-ml. portions of chloroform, filtering the extracts through a pledget of cotton into a 150-ml. flask. Evaporate the chloroform in a current of warm air, and add 5 ml. of pyridine and 3 ml. of acetic anhydride to the dry residue. Connect the flask to a reflux condenser, reflux for 10 minutes, cool, and proceed as directed in the *Assay* under *Monobenzone*, page 462, beginning with "Transfer the contents of the flask . . . ."

Packaging and storage—Preserve Monobenzone Ointment in tight containers and avoid prolonged exposure to temperatures above 30°.

Ointment available—Monobenzone Ointment usually available contains 20 percent monobenzone.

Category—See Monobenzone.

Monoethanolamine

$HOCH_2CH_2NH_2$

2-Aminoethanol

C_2H_7NO Mol. wt. 61.08

Monoethanolamine contains not less than 98.0 percent and not more than 100.5 percent, by weight, of C_2H_7NO.

Description—Monoethanolamine is a clear, colorless, moderately viscous liquid having a distinctly ammoniacal odor.

Solubility—Monoethanolamine is miscible with water, with acetone, with alcohol, with glycerin, and with chloroform. It is immiscible with ether, with solvent hexane and with fixed oils, although it will dissolve many essential oils.

Specific gravity, page 866—The specific gravity of Monoethanolamine is not less than 1.013 and not more than 1.016.

Distilling range, page 782—Not less than 95 percent of Monoethanolamine distils between 167° and 173°.

Assay—Accurately weigh a glass-stoppered weighing bottle containing 25 ml. of water. Add 1 g. of Monoethanolamine, and weigh. Add 3 drops of a mixed indicator of bromocresol green T.S. and methyl red T.S. (5 in 6), mix and titrate with 0.5 *N* hydrochloric acid. Each ml. of 0.5 *N* hydrochloric acid is equivalent to 30.54 mg. of C_2H_7NO.

Packaging and storage—Preserve Monoethanolamine in tight, light-resistant containers.

CATEGORY—Surfactant.

Morphine and Atropine Sulfates Tablets

Morphine and Atropine Sulfates Tablets contain not less than 91.0 percent and not more than 109.0 percent of the labeled amounts of $(C_{17}H_{19}NO_3)_2 . H_2SO_4 . 5H_2O$ (morphine sulfate) and of $(C_{17}H_{23}NO_3)_2 . H_2SO_4 . H_2O$ (atropine sulfate).

Identification—Digest a quantity of finely powdered Morphine and Atropine Sulfates Tablets, equivalent to about 20 mg. of morphine sulfate, with 15 ml. of water and 5 ml. of diluted sulfuric acid for 1 hour. Filter, if necessary, and wash any undissolved residue with a few ml. of water. Render the filtrate alkaline with ammonia T.S., extract with several small portions of a mixture of 4 volumes of chloroform and 1 volume of alcohol, and evaporate the solution to dryness on a steam bath. The resulting residue responds to *Identification tests A, B, C,* and *D.*

A: To 1 mg. of residue in a porcelain crucible or small dish add 0.5 ml. of sulfuric acid-formaldehyde T.S.: an intense purple color is produced at once, gradually assuming a blue color (*difference from codeine which gives at once an intense violet-blue color, and from hydromorphone which gives at first a yellow to brown color changing to pink and then to purplish red*).

B: To 1 mg. of residue in a porcelain crucible or small dish add 0.5 ml. of sulfuric acid containing in each ml. 5 mg. of molybdic acid: an intense purple color is produced at once (*difference from codeine which gives at first a pale greenish yellow color quickly changing to green and, after several minutes, becoming dark olive-green; also difference from hydromorphone which produces an intense violet-blue color at once*).

C: Dissolve 2 mg. of residue in 2 ml. of water and add to the solution a few drops of potassium ferricyanide T.S. containing in each ml. 1 drop of ferric chloride T.S.: a deep blue color is produced at once (*hydromorphone gives the same color; with codeine and ethylmorphine, no blue color is formed even after a few minutes; papaverine gives a yellow precipitate*).

D: To a solution of 5 mg. of residue in 5 ml. of sulfuric acid in a test tube add 1 drop of ferric chloride T.S., mix and heat in boiling water for 2 minutes: a blue color is produced which, upon the addition of a drop of nitric acid, changes to dark red-brown (*codeine and ethylmorphine give the same color reactions, but hydromorphone and papaverine do not produce this color change*).

E: Barium chloride T.S. produces in a filtered solution of Morphine and Atropine Sulfates Tablets a white precipitate, insoluble in hydrochloric acid.

F: Dissolve a sufficient number of Morphine and Atropine Sulfates Tablets to represent 600 mcg. of atropine sulfate in 10 ml. of water, and filter the solution. Instil 1 drop of this solution into a cat's eye: the pupil shows noticeable dilation within 2 hours.

Disintegration, page 878—The disintegration time limit for Morphine and Atropine Sulfates Tablets is 15 minutes.

Content uniformity, page 799—Morphine and Atropine Sulfates Tablets meet the requirements of the content uniformity test for tablets when tested for atropine sulfate content by *Method I,* and for morphine sulfate content by *Method II* using the following special procedure: Transfer one tablet to a 50-ml. volumetric flask containing 25 ml. of water, and shake the flask until the tablet is dissolved. Dilute to volume with water, mix, and filter, discarding the first 10 ml. of filtrate. Dilute a portion of the subsequent filtrate, if necessary, with water to provide a solution containing approximately 150 mcg. of morphine sulfate per ml. Concomitantly determine the absorbance of this solution and of a standard solution of USP Morphine Sulfate, in the same medium at a concentration of about 150 mcg. per ml., in 1-cm. cells, at the maximum at about 286 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $(C_{17}H_{19}NO_3)_2 . H_2SO_4 . 5H_2O$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of morphine sulfate in the tablet; D is the exact concentration, in mcg. per ml., of morphine sulfate in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the standard solution.

Assay for atropine sulfate—

Internal standard solution—Prepare a solution in chloroform containing 80.0 mcg. of anthracene in each ml.

Standard preparation—Transfer about 50 mg. of USP Atropine Sulfate Reference Standard, accurately weighed, to a 25-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with water, and mix. Transfer 10.0 ml. of this last solution to a second 100-ml. volumetric flask, dilute to volume with water, and mix. Transfer 20.0 ml. of the final dilution to a 60-ml. separator, and continue as directed under *Assay preparation*, beginning with "... and make the solution alkaline by the addition of ammonia T.S."

Assay preparation—Weigh and finely powder not less than 20 Morphine and Atropine Sulfates Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 400 mcg. of atropine sulfate, to a 60-ml. separator containing 20 ml. of water, shake to dissolve the powder, and make the solution alkaline by the addition of ammonia T.S. Extract the solution with three 10-ml. portions of chloroform, and evaporate the combined extracts to a volume of about 3 ml. Quantitatively transfer the residual liquid to a small glass-stoppered tube with the aid of about 5 ml. of chloroform, and evaporate just to dryness. Transfer 1.0 ml. of *Internal standard solution* to the tube, stopper, and warm on a steam bath to dissolve the atropine. Use the resultant solution as directed in the *Procedure*.

Procedure—Inject a suitable volume of the *Standard preparation* into a suitable gas chromatograph equipped with a flame-ionization detector, and record the chromatogram. Under typical conditions, the instrument contains a 1.8-meter × 6-mm. (outside diameter) glass column packed with 5 percent methyl silicone gum on 80 to 100-mesh washed chromatographic siliceous earth. The column is maintained at 225° and the injector port and the detector block at 280°; helium is used as the carrier gas at a flow rate of 50 ml. per minute.

Measure the peak height of each component, recording the height of the anthracene peak as P_1 and that of the atropine peak as P_2.

Similarly, inject a suitable volume of the *Assay preparation* into the chromatograph, and record the chromatogram under the same conditions as described for the *Standard preparation*. Measure the peak height of each component, recording the height of the anthracene peak as p_1 and that of the atropine peak as p_2.

Calculate the quantity, in mcg., of $(C_{17}H_{23}NO_3)_2 . H_2SO_4 . H_2O$ in the portion of Tablets taken by the formula $C \times (p_2 \times P_1)/(p_1 \times P_2)$, in which C is the exact equivalent concentration, in mcg. per ml., of atropine sulfate in the *Standard preparation*.

Assay for morphine sulfate—Weigh and finely powder not less than 20 Morphine and Atropine Sulfates Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 130 mg. of morphine sulfate, to a separator, add 5 ml. of water, agitate the mixture gently, and then dissolve it as completely as possible in 10 ml. of a 3 percent solution of sodium hydroxide saturated with sodium chloride. Wash the solution with two 15-ml. portions of ether, discard the washings, add hydrochloric acid until the solution is neutral to litmus, and then add an additional 0.5 ml. of the acid. Add 5 ml. of alcohol, followed by 30 ml. of a mixture of 9 volumes of chloroform and 1 volume of alcohol. Carefully neutralize the solution with stronger ammonia water, and add an additional 5 drops of the ammonia. Extract the alkaloid completely with successive portions of the chloroform-alcohol solvent. Wash the combined extracts with 1 ml. of water, and extract the wash water twice with small portions of the chloroform-alcohol solvent. Filter the combined chloroform extracts into a small beaker, and evaporate the filtrate on a steam bath, with the aid of a current of air, until the residue is nearly dry; dissolve the residue in 10.0 ml. of 0.05 *N* sulfuric acid, warming to aid solution, add 3 drops of methyl red T.S. and titrate the excess acid with 0.02 *N* sodium hydroxide. Each ml. of 0.05 *N* sulfuric acid is equivalent to 18.97 mg. of $(C_{17}H_{19}NO_3)_2 . H_2SO_4 . 5H_2O$.

Packaging and storage—Preserve Morphine and Atropine Sulfates Tablets in tight containers.

Tablets available—Morphine and Atropine Sulfates Tablets usually available contain the following amounts of morphine sulfate: 8, 10, 15, and 30 mg.; and of atropine sulfate: 400 mcg.

CATEGORY—Analgesic (narcotic); anticholinergic.

USUAL INDIVIDUAL DOSE RANGE OF MORPHINE SULFATE—**5** to **20 mg.**; OF ATROPINE SULFATE—**300 mcg.** to **1.2 mg.**

Myristica Oil

Myristica Oil is the volatile oil distilled with steam from the dried kernels of the ripe seeds of *Myristica fragrans* Houttuyn (Fam. *Myristicaceæ*).

Description—Myristica Oil is a colorless or pale yellow liquid, having the characteristic odor and taste of nutmeg.

Solubility—One volume of Myristica Oil dissolves in 1 volume of alcohol.

Solubility in 90 percent alcohol—One volume of East Indian Myristica Oil dissolves in 3 volumes of 90 percent alcohol. One volume of West Indian Myristica Oil dissolves in 4 volumes of 90 percent alcohol.

Specific gravity, page 866—The specific gravity of Myristica Oil is not less than 0.880 and not more than 0.910 for East Indian Oil, and not less than 0.854 and not more than 0.880 for West Indian Oil.

Angular rotation, page 822—The angular rotation of Myristica Oil, determined in a 100-mm. tube, is between +8° and +30° for East Indian Oil, and between +25° and +45° for West Indian Oil.

Refractive index, page 858—The refractive index of Myristica Oil is not less than 1.474 and not more than 1.488 for East Indian Oil, and not less than 1.469 and not more than 1.476 for West Indian Oil, at 20°.

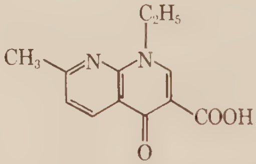
Nonvolatile residue—Evaporate 3 ml. of Myristica Oil in a tared, 40 × 80-mm. glass crystallizing dish on a steam bath for 5 hours. Continue heating at 105° for 1 hour. Cool in a desiccator, and weigh: the weight of the residue does not exceed 60 mg. for East Indian Oil (2 per cent, w/v), and 50 mg. for West Indian Oil (1.7 percent, w/v).

Packaging and storage—Preserve Myristica Oil in tight containers.

Labeling—Label Myristica Oil to indicate whether it is East Indian or West Indian Oil.

Category—Flavor.

Nalidixic Acid*



1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic Acid

$C_{12}H_{12}N_2O_3$ Mol. wt. 232.24

Nalidixic Acid contains not less than 98.0 percent and not more than 102.0 percent of $C_{12}H_{12}N_2O_3$, calculated on the dried basis.

Description—Nalidixic Acid occurs as a white to slightly yellow, crystalline, odorless powder.

Solubility—Nalidixic Acid is practically insoluble in water. It is slightly soluble in alcohol, soluble in chloroform, and very slightly soluble in ether. It is soluble in solutions of fixed alkali hydroxides and carbonates.

Melting range, *Class Ia,* page 815—Nalidixic Acid melts between 225° and 231°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Nalidixic Acid, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Nalidixic Acid Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Nalidixic Acid in 0.01 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Nalidixic Acid Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance occurring at about 258 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Nalidixic Acid at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Nalidixic Acid yields not more than 0.2 percent of residue on ignition. Retain the residue from a 1-g. sample for the *Heavy metals test.*

Heavy metals, page 806—Dissolve the residue resulting from the *Residue on*

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* Patent pending. See notice, page ii.

ignition test in a few ml. of hot nitric acid, and evaporate to dryness on a steam bath. Dissolve the residue in 2 ml. of diluted acetic acid and add 23 ml. of water: the heavy metals limit for Nalidixic Acid is 20 parts per million.

Assay—Dissolve about 250 mg. of Nalidixic Acid, accurately weighed, in 30 ml. of dimethylformamide which has been previously neutralized to thymolphthalein T.S., and titrate with 0.1 *N* lithium methoxide, using a magnetic stirrer. Each ml. of 0.1 *N* lithium methoxide is equivalent to 23.22 mg. of $C_{12}H_{12}N_2O_3$.

Packaging and storage—Preserve Nalidixic Acid in tight containers.

Category—Antibacterial.

Usual dose—**1 g.** four times a day for 1 to 2 weeks. Thereafter, for prolonged treatment, the dose may be reduced to **500 mg.** four times a day.

Nalidixic Acid Tablets

Nalidixic Acid Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{12}H_{12}N_2O_3$.

Identification—

A: The ultraviolet absorption spectrum of the sample solution, prepared as directed in the *Assay*, exhibits maxima and minima at the same wavelengths as that of the Reference Standard solution, prepared as directed in the *Assay*, similarly measured.

B: Dissolve a portion of finely powdered Nalidixic Acid Tablets, equivalent to about 100 mg. of nalidixic acid, in 50 ml. of chloroform, shake for 15 minutes, and filter. Evaporate the filtrate to dryness on a steam bath, and dry the residue at 105° to constant weight: the nalidixic acid so obtained melts between 225° and 231°, page 814.

Weight variation, page 901—Nalidixic Acid Tablets meet the requirements of the weight variation test for tablets.

Disintegration, page 878—The disintegration time limit for Nalidixic Acid Tablets is 30 minutes.

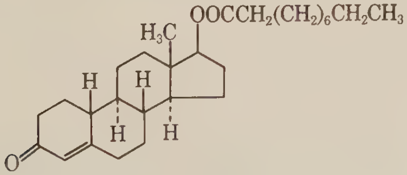
Assay—Weigh and finely powder not less than 20 Nalidixic Acid Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 150 mg. of nalidixic acid, to a separator, add 100 ml. of chloroform, and shake for 5 minutes. Extract the mixture with five 20-ml. portions of sodium hydroxide T.S., collecting each portion in a 200-ml. volumetric flask. Dilute to volume with sodium hydroxide T.S., mix, and filter, discarding the first 20 ml. of filtrate. Transfer 10.0 ml. of the subsequent filtrate to a 100-ml. volumetric flask, dilute to volume with water, and mix. Finally, transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Nalidixic Acid Reference Standard, in the same medium, at a concentration of about 7.5 mcg. per ml., in 1-cm. cells, at the maximum at about 258 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{12}H_{12}N_2O_3$ in the portion of Tablets taken by the formula $20C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Nalidixic Acid Tablets in tight containers.

Tablets available—Nalidixic Acid Tablets usually available contain the following amounts of nalidixic acid: 250 and 500 mg.

Category and Dose—See Nalidixic Acid.

Nandrolone Decanoate*



17β-Hydroxyestr-4-en-3-one Decanoate

$C_{28}H_{44}O_3$ Mol. wt. 428.66

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* Patented. See notice, page ii.

Nandrolone Decanoate contains not less than 96.0 percent and not more than 104.0 percent of $C_{28}H_{44}O_3$, calculated on the dried basis.

Description—Nandrolone Decanoate occurs as a fine, white to creamy white, crystalline powder. It is odorless or may have a slight odor.

Solubility—Nandrolone Decanoate is soluble in chloroform, in alcohol, in acetone, and in vegetable oils. It is practically insoluble in water.

Completeness and clarity of solution—A solution of Nandrolone Decanoate (1 in 50) in dioxane is clear.

Identification—Prepare a solution of Nandrolone Decanoate in acetone containing 5 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of an acetone solution of NF Nandrolone Decanoate Reference Standard containing 5 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of *n*-heptane and acetone (3:1) until the solvent front has moved about 15 cm. from the origin. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid in alcohol (1 in 50) and heating at 110° for 15 minutes in an oven. The R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Melting range, *Class Ia,* page 815—Nandrolone Decanoate melts between 33° and 37°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Nandrolone Decanoate, previously dried in vacuum over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Nandrolone Decanoate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Nandrolone Decanoate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Nandrolone Decanoate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance occurring at about 239 mµ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Nandrolone Decanoate, previously dried in vacuum over silica gel for 4 hours, determined in a solution in dioxane containing 100 mg. of Nandrolone Decanoate in 10 ml., is between +32° and +36°.

Loss on drying, page 814—Dry Nandrolone Decanoate in vacuum over silica gel for 4 hours: it loses not more than 0.5 percent of its weight.

Foreign steroids and other impurities—*Standard preparation*—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Nandrolone Decanoate Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Nandrolone Decanoate previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of *n*-heptane and acetone (3:1), and determining the absorbance at the maximum at about 239 mµ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Nandrolone Decanoate taken: not more than 3 percent is found.

Assay—

Isoniazid reagent—Dissolve 500 mg. of isonicotinic acid hydrazide in about 250 ml. of methanol, add 0.63 ml. of hydrochloric acid, dilute to 500.0 ml. with methanol, and mix.

Standard preparation—Transfer about 25 mg. of NF Nandrolone Decanoate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Dilute 5.0 ml. of this solution to 50.0 ml. with methanol, and mix.

Assay preparation—Transfer about 25 mg. of Nandrolone Decanoate, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Dilute 5.0 ml. of this solution to 50.0 ml. with methanol, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation,* of the *Assay preparation,* and of methanol to serve as the blank to separate 10-ml. volumetric flasks, dilute each to volume with *Isoniazid reagent,* and mix. Allow the flasks to stand for 1 hour with occasional shaking. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 380 mµ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg, of $C_{28}H_{44}O_3$ in the Nandrolone Decanoate taken by the formula $C \times$

(A_U/A_S), in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Nandrolone Decanoate in tight, light-resistant containers in a refrigerator.

Category—Androgen.

Usual dose—Intramuscular, **50 to 100 mg.** every 3 to 4 weeks.

Nandrolone Decanoate Injection

Nandrolone Decanoate Injection is a sterile solution of nandrolone decanoate in sesame oil, with a suitable preservative. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{28}H_{44}O_3$.

Identification—Dilute a volume of Nandrolone Decanoate Injection with acetone to provide a solution containing approximately 5 mg. of nandrolone decanoate per ml. This solution meets the requirements of the *Identification test* under *Nandrolone Decanoate*, page 467, using 5-µl. portions of the sample and of the Reference Standard solutions.

Other requirements—Nandrolone Decanoate Injection meets the requirements under *Injections*, page 810.

Assay—

Isoniazid reagent and *standard preparation*—Prepare as directed in the *Assay* under *Nandrolone Decanoate*, page 467.

Assay preparation—Transfer to a 200-ml. volumetric flask an accurately measured volume of Nandrolone Decanoate Injection, equivalent to about 50 mg. of nandrolone decanoate, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, add chloroform to volume, and mix.

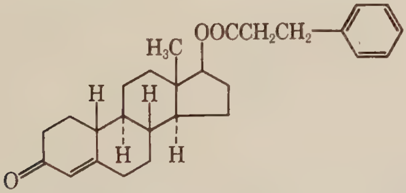
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Nandrolone Decanoate*, page 467. Calculate the quantity, in mg., of $C_{28}H_{44}O_3$ in each ml. of the Injection by the formula $2 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Nandrolone Decanoate Injection in single-dose or multiple-dose containers, preferably of Type I glass, protected from light.

Injections available—Nandrolone Decanoate Injection usually available contains the following amounts of nandrolone decanoate: 50 mg. in 1 ml.; 100 mg. in 2 ml.

Category and Dose—See Nandrolone Decanoate.

Nandrolone Phenpropionate*



17β-Hydroxyestr-4-en-3-one Hydrocinnamate

$C_{27}H_{34}O_3$ Mol. wt. 406.57

Nandrolone Phenpropionate contains not less than 97.0 percent and not more than 103.0 percent of $C_{27}H_{34}O_3$, calculated on the dried basis.

Description—Nandrolone Phenpropionate occurs as a fine, white to creamy white, crystalline powder. It has a slight characteristic odor.

Solubility—Nandrolone Phenpropionate is practically insoluble in water. It is soluble in alcohol, in chloroform, in dioxane, and in vegetable oils.

Identification—Prepare a solution of Nandrolone Phenpropionate in acetone containing 5 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of an acetone solution of NF Nandrolone Phenpropionate Reference Standard containing 5 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of *n*-heptane and acetone (2:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 50) in alcohol and heating at 110° for 15 minutes: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

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* Patented. See notice, page ii.

Melting range, *Class Ia,* page 815—Nandrolone Phenpropionate melts between 95° and 99°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Nandrolone Phenpropionate, previously dried in vacuum over phosphorus pentoxide at 80° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Nandrolone Phenpropionate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Nandrolone Phenpropionate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Nandrolone Phenpropionate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 239 mµ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Nandrolone Phenpropionate, previously dried in vacuum over phosphorus pentoxide at 80° for 3 hours, determined in a solution in dioxane containing 200 mg. in each 10 ml., is between +48° and +51°.

Loss on drying, page 814—Dry Nandrolone Phenpropionate in vacuum over phosphorus pentoxide at 80° for 3 hours: it loses not more than 0.5 percent of its weight.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Nandrolone Phenpropionate Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Nandrolone Phenpropionate, previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of *n*-heptane and acetone (3:1), and determining the absorbance at the maximum at about 239 mµ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Nandrolone Phenpropionate taken: not more than 3 percent is found.

Assay—

Isoniazid reagent—Dissolve 500 mg. of isonicotinic acid hydrazide in about 250 ml. of methanol, add 0.63 ml. of hydrochloric acid, dilute to 500.0 ml. with methanol, and mix.

Standard preparation—Transfer about 25 mg. of NF Nandrolone Phenpropionate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 5.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with methanol, and mix.

Assay preparation—Transfer about 25 mg. of Nandrolone Phenpropionate, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 5.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with methanol, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation,* of the *Assay preparation,* and of methanol to serve as the blank to separate 10-ml. volumetric flasks, dilute each flask to volume with the *Isoniazid reagent,* and mix. Allow the flasks to stand for 1 hour with occasional shaking. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 380 mµ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{27}H_{34}O_3$ in the Nandrolone Phenpropionate taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Nandrolone Phenpropionate in tight, light-resistant containers.

CATEGORY—Androgen.

USUAL DOSE—Intramuscular, **25** to **50 mg.** each week.

Nandrolone Phenpropionate Injection

Nandrolone Phenpropionate Injection is a sterile solution of nandrolone phenpropionate in a suitable oil. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{27}H_{34}O_3$.

Identification—Dilute Nandrolone Phenpropionate Injection with acetone to obtain a solution containing 5 mg. of nandrolone phenpropionate in each ml. Proceed as directed for *Identification* under *Nandrolone Phenpropionate*, page 469, beginning with "On a suitable thin-layer chromatographic plate . . . ."

Other requirements—Nandrolone Phenpropionate Injection meets the requirements under *Injections*, page 810.

Assay—

Isoniazid reagent—Prepare as directed in the *Assay* under *Nandrolone Phenpropionate*, page 469.

Standard preparation—Transfer about 25 mg. of NF Nandrolone Phenpropionate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add chloroform to volume, and mix. Transfer 5.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparation—Transfer to a 200-ml. volumetric flask an accurately measured volume of Nandrolone Phenpropionate Injection, equivalent to about 50 mg. of nandrolone phenpropionate, add chloroform to volume, and mix. Transfer 5.0 ml. of this solution to a 50-ml. volumetric flask, add chloroform to volume, and mix.

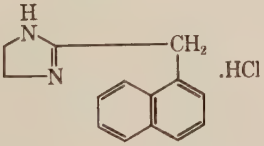
Procedure—Transfer 5.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of chloroform to separate 10-ml. volumetric flasks, and dilute each flask to volume with the *Isoniazid reagent*, and mix. Allow the flasks to stand for 1 hour with occasional shaking. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 380 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{27}H_{34}O_3$ in each ml. of the Injection taken by the formula $2 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Nandrolone Phenpropionate Injection in single-dose or multiple-dose containers, preferably of Type I glass, protected from light.

Injections available—Nandrolone Phenpropionate Injection usually available contains the following amounts of nandrolone phenpropionate: 25 mg. in 1 ml.; 100 mg. in 2 ml.; 125 mg. in 5 ml.

Category and Dose—See Nandrolone Phenpropionate.

Naphazoline Hydrochloride



2-(1-Naphthylmethyl)-2-imidazoline Monohydrochloride

$C_{14}H_{14}N_2 . HCl$ Mol. wt. 246.74

Naphazoline Hydrochloride, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{14}H_{14}N_2 . HCl$.

Description—Naphazoline Hydrochloride occurs as a white, crystalline powder. It is odorless and has a bitter taste.

Solubility—Naphazoline Hydrochloride is freely soluble in water and in alcohol. It is very slightly soluble in chloroform, and practically insoluble in ether.

Identification—

A: Dissolve about 300 mg. of Naphazoline Hydrochloride in 25 ml. of water in a separator, make the solution alkaline with sodium hydroxide T.S., and extract with two 25-ml. portions of ether. Evaporate the ether extract nearly to dryness on a steam bath, complete the evaporation in a current of warm air, and dry the crystalline residue at 80° for 1 hour: the naphazoline so obtained melts between 117° and 120°, page 814.

B: Dissolve about 20 mg. of the residue from *Identification test A* in a few drops of diluted hydrochloric acid, add 5 ml. of water, then add 2 ml. of ammonium reineckate T.S.: a mauve, crystalline precipitate is formed.

C: A solution of Naphazoline Hydrochloride (1 in 100) responds to the test for *Chloride*, page 808.

Melting range, page 814—Naphazoline Hydrochloride melts between 253° and 258°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Naphazoline Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Naphazoline Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Naphazoline Hydrochloride in methanol exhibits maxima and minima at the same wavelengths as that of NF Naphazoline Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 280 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Naphazoline Hydrochloride (1 in 100) in carbon dioxide-free water is not less than 6.1, and the solution is clear and colorless.

Loss on drying, page 814—Dry Naphazoline Hydrochloride at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Naphazoline Hydrochloride yields not more than 0.2 percent of residue on ignition.

Assay—Dissolve about 300 mg. of Naphazoline Hydrochloride, previously dried at 105° for 2 hours and accurately weighed, in 5 ml. of water, and add 10 ml. of sodium hydroxide T.S., previously saturated with sodium chloride. Completely extract with six or more 20-ml. portions of ether. Wash the combined ether extracts with two 5-ml. portions of water, extract the combined water washings with 10 ml. of ether, and add this to the combined ether extracts. Evaporate the ether to about 10 ml., add 30.0 ml. of 0.05 *N* hydrochloric acid, warm gently until the remainder of the ether is expelled, cool, add methyl red T.S., and titrate the excess acid with 0.05 *N* sodium hydroxide. Each ml. of 0.05 *N* hydrochloric acid is equivalent to 12.34 mg. of $C_{14}H_{14}N_2 . HCl$.

Packaging and storage—Preserve Naphazoline Hydrochloride in tight, light-resistant containers.

CATEGORY—Adrenergic (vasoconstrictor).

APPLICATION—To the nasal mucosa, 2 drops of a 0.05 percent solution no more frequently than every 3 hours.

Naphazoline Hydrochloride Solution

Naphazoline Hydrochloride Solution is a solution of naphazoline hydrochloride in water adjusted to a suitable pH and tonicity. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_{14}N_2 . HCl$.

Identification—Transfer to a separator a volume of Naphazoline Hydrochloride Solution, equivalent to about 25 mg. of naphazoline hydrochloride, add 5 ml. of sodium hydroxide T.S., saturate with sodium chloride, and extract with two 25-ml. portions of ether. Wash the ether solution with 5 ml. of water, then filter the ether through a small paper filter. Evaporate the filtrate to about 5 ml., transfer the residual solution to a 10- to 15-ml. beaker, allow to evaporate spontaneously, and dry the residue at 80° for 1 hour: the naphazoline so obtained melts between 115° and 120°, page 814.

Assay—Transfer to a 100-ml. volumetric flask an accurately measured volume of Naphazoline Hydrochloride Solution, equivalent to about 2 mg. of naphazoline hydrochloride, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Naphazoline Hydrochloride Reference Standard in the same medium, at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 280 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{14}H_{14}N_2 . HCl$ in each ml. of the Solution taken by the formula $0.1 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., V is the volume, in ml., of the Solution taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Naphazoline Hydrochloride Solution in tight, light-resistant containers.

Solution available—Naphazoline Hydrochloride Solution usually available contains 0.05 percent of naphazoline hydrochloride.

Category—See Naphazoline Hydrochloride.

Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream

Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream contains an amount of neomycin sulfate equivalent to not less than 90.0 percent and not more than 135.0 percent of the labeled amount of neomycin base, and an amount of $C_{22}H_{28}FNa_2O_8P$ (dexamethasone sodium phosphate) equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{22}H_{30}FO_8P$ (dexamethasone phosphate). Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Identification—

A: Heat 1 ml. of the *Assay preparation* with 5 ml. of phenylhydrazine reagent (prepared as described under *Assay*) at 70° for 2 hours: a yellow color develops.

B: Place 5 ml. of the *Assay preparation* in a 50-ml. glass-stoppered tube. Incubate at 37° for 45 minutes with 5 ml. of alkaline phosphatase solution, prepared by dissolving 50 mg. of alkaline phosphatase in 50 ml. of a buffer solution pH 9.0 (made by dissolving 3.1 g. of boric acid, 203 mg. of magnesium chloride, and 860 mg. of sodium hydroxide in sufficient water to make 1000 ml.) After the incubation add 25 ml. of methylene chloride, and shake for 2 minutes. Evaporate 15 ml. of the methylene chloride extract to dryness, dissolve the residue in 1 ml. of methylene chloride, and apply 5 µl. of the solution to a suitable thin-layer chromatographic plate (see page 791) coated with a 0.25-mm. layer of silica gel G. Apply to the same plate 5 µl. of a methylene chloride solution containing 300 mcg. per ml. of USP Dexamethasone Reference Standard. Develop the chromatogram in a chamber completely lined with a strip of filter paper 18 cm. wide, the developing solvent consisting of a mixture of chloroform, acetone, and water (50:50:1). When the solvent front has ascended 15 cm. from the starting line, remove the plate from the chamber, allow it to dry, and spray it with dilute sulfuric acid (1 in 2). Heat at 105° until brown or black spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Assay for dexamethasone phosphate—

Standard preparation—Transfer about 120 mg. of USP Dexamethasone Sodium Phosphate Reference Standard, equivalent to about 100 mg. of dexamethasone phosphate, accurately weighed, to a 100-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix. Transfer 1.0 ml. of this solution to a 125-ml. separator containing 15 ml. of sodium chloride solution (1 in 10), and continue as directed under *Assay preparation*, beginning with "Extract with two 15-ml. portions of methylene chloride. . . ."

Assay preparation—Transfer an accurately weighed portion of Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream, equivalent to about 1 mg. of dexamethasone phosphate, to a 125-ml. separator containing 15 ml. of sodium chloride solution (1 in 10), and shake to disperse the sample. Extract with two 15-ml. portions of methylene chloride, and discard the extracts. To the separator add 0.5 ml. of hydrochloric acid and 10.0 ml. of tri-*n*-butyl phosphate, shake for 5 minutes, and filter the tri-*n*-butyl phosphate phase. Use the filtrate as directed in the *Procedure*.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate glass-stoppered tubes, and transfer 2.0 ml. of tri-*n*-butyl phosphate to a third tube to serve as the blank. Add to each tube 5.0 ml. of freshly prepared phenylhydrazine reagent, consisting of 40 ml. of water, 60 ml. of sulfuric acid, 50 ml. of isopropyl alcohol, and 65 mg. of phenylhydrazine hydrochloride. Stopper loosely and place in a water bath at 70° for 2 hours, and cool. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 410 mµ, with a suitable spectrophotometer, using the reagent blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{30}FO_8P$ in the portion of the Cream taken by the formula $0.01C \times 0.9148 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Dexamethasone Sodium Phosphate Reference Standard in the *Standard preparation*, calculated on the water-free and alcohol-free basis and 0.9148 is the factor for converting dexamethasone sodium phosphate to dexamethasone phosphate.

Packaging and storage—Preserve Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream in collapsible tubes, or in tight containers.

Cream available—Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream usually available contains neomycin sulfate equivalent to 0.35 percent of neomycin base and dexamethasone sodium phosphate equivalent to 0.1 percent of dexamethasone phosphate.

Category—Glucocorticoid; antibacterial.

Application—Topically to the affected area two or three times a day.

Neomycin Sulfate and Hydrocortisone Acetate Lotion

Neomycin Sulfate and Hydrocortisone Acetate Lotion is neomycin sulfate and hydrocortisone acetate suspended in a suitable aqueous vehicle. It contains an amount of neomycin sulfate equivalent to not less than 90.0 percent and not more than 135.0 percent of the labeled amount of neomycin base, and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of hydrocortisone acetate ($C_{23}H_{32}O_6$). Neomycin Sulfate and Hydrocortisone Acetate Lotion conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Identification—Evaporate 25 ml. of the *Assay preparation* from the *Assay* on a steam bath just to dryness, and dissolve the residue in 1 ml. of methanol. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 10 µl. of this solution and 10 µl. of a methanol solution of USP Hydrocortisone Acetate Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform, methanol, and water (180:15:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under shortwave ultraviolet light: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution (*presence of hydrocortisone acetate*).

Assay for hydrocortisone acetate—

Standard preparation—Prepare as directed for *Standard preparation* under *Steroid Assay*, page 876, using USP Hydrocortisone Acetate Reference Standard.

Assay preparation—Transfer an accurately weighed portion of Neomycin Sulfate and Hydrocortisone Acetate Lotion, equivalent to about 20 mg. of hydrocortisone acetate, to a separator, and add 15 ml. of water. Extract with four 25-ml. portions of chloroform, filtering each portion through chloroform-washed cotton into a 200-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 20.0 ml. of this solution into a 100-ml. volumetric flask. Add chloroform to volume, and mix. Pipet 10.0 ml. of this solution into a 50-ml. glass-stoppered conical flask, evaporate on a steam bath just to dryness, and dissolve the residue in 20.0 ml. of alcohol.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{23}H_{32}O_6$ in the portion of the Lotion taken by the formula $2C \times (A_U/A_S)$.

Packaging and storage—Preserve Neomycin Sulfate and Hydrocortisone Acetate Lotion in tight containers.

Lotions available—Neomycin Sulfate and Hydrocortisone Acetate Lotion usually available contains 0.35 percent neomycin base with 0.5 percent or 1 percent of hydrocortisone acetate.

Category—Glucocorticoid; antibacterial.

Application—Topically to the affected area one to three times a day.

Neomycin Sulfate, Polymyxin B Sulfate and Gramicidin Ophthalmic Solution

Neomycin Sulfate, Polymyxin B Sulfate and Gramicidin Ophthalmic Solution is a sterile isotonic solution of polymyxin B sulfate, neomycin sulfate and gramicidin. It contains not less than 90.0 percent and not more than 130.0 percent of the labeled amounts of neomycin base, polymyxin B sulfate and gramicidin. It conforms to the regulations of the federal Food and Drug Administration concerning the certification of antibiotic drugs.

Packaging and storage—Preserve Neomycin Sulfate, Polymyxin B Sulfate and Gramicidin Ophthalmic Solution in tight, light-resistant containers.

Solution available—Neomycin Sulfate, Polymyxin B Sulfate and Gramicidin Ophthalmic Solution usually available contains in each ml.: 5000 units of polymyxin B sulfate; 2 mg. of neomycin base; and 0.02 to 0.025 mg. of gramicidin.

Category—Local anti-infective.

Application—One or two drops in the eye, two to four times daily.

Neomycin Sulfate, Polymyxin B Sulfate and Zinc Bacitracin Ointment

Neomycin Sulfate, Polymyxin B Sulfate and Zinc Bacitracin Ointment contains not less than 90.0 percent of the labeled amounts of neomycin base, polymyxin B sulfate, and zinc bacitracin. It conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

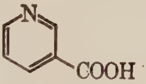
Packaging and storage—Preserve Neomycin Sulfate, Polymyxin B Sulfate and Zinc Bacitracin Ointment in well-closed containers.

Ointments available—Neomycin Sulfate, Polymyxin B Sulfate and Zinc Bacitracin Ointment usually available contains in each g., the following: polymyxin B sulfate: 5000 units; neomycin base: 3.5 mg.; and zinc bacitracin: 400 units; or polymyxin B sulfate: 8000 units; neomycin base: 3 mg.; and zinc bacitracin: 400 units.

Category—Local anti-infective.

Application—Topical, to the affected area two to five times daily.

Niacin



Nicotinic Acid

$C_6H_5NO_2$ Mol. wt. 123.11

Niacin contains not less than 99.5 percent and not more than 101.0 percent of $C_6H_5NO_2$, calculated on the dried basis.

Description—Niacin occurs as white crystals or crystalline powder. It is odorless or has a slight odor. It melts at about 235°.

Solubility—Niacin is sparingly soluble in water. It is freely soluble in boiling water and in boiling alcohol, and also in solutions of alkali hydroxides and carbonates. It is practically insoluble in ether.

Identification—

A: Triturate Niacin with twice its weight of 2,4-dinitrochlorobenzene. Gently heat about 10 mg. of the mixture in a test tube until melted, and continue the heating for a few seconds longer. Cool, and add 3 ml. of alcoholic potassium hydroxide T.S.: a deep red to deep wine-red color is produced.

B: Dissolve about 50 mg. of Niacin in 20 ml. of water, neutralize to litmus paper with 0.1 *N* sodium hydroxide, and add 3 ml. of cupric sulfate T.S.: a blue precipitate gradually forms.

Infrared absorption. page 866—The infrared absorption spectrum of a potassium bromide dispersion of Niacin, previously dried at 105° for 1 hour, exhibits maxima only at the same wavelengths as that of NF Niacin Reference Standard, similarly measured.

Ultraviolet absorption, page 866—Determine the absorbance of a water solution of Niacin, containing 20 mcg. per ml., in a 1-cm. cell, at 237 mμ and 262 mμ, with a suitable spectrophotometer, using water as the blank. The ratio A_{237}/A_{262} is 0.37 ± 0.02.

Loss on drying, page 814—Dry Niacin at 105° for 1 hour: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Niacin yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—A 500-mg. portion of Niacin shows no more chloride than corresponds to 0.15 ml. of 0.02 *N* hydrochloric acid (0.02 percent).

Sulfate, page 784—A 500-mg. portion of Niacin shows no more sulfate than corresponds to 0.1 ml. of 0.02 *N* sulfuric acid (0.02 percent).

Heavy metals, page 806—Mix 500 mg. of Niacin with 2 ml. of diluted acetic acid, add water to make 25 ml., heat gently until solution is complete, and cool: the heavy metals limit for Niacin is 20 parts per million.

Assay—Dissolve about 300 mg. of Niacin, accurately weighed, in about 50 ml. of water, add phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 12.31 mg. of $C_6H_5NO_2$.

Packaging and storage—Preserve Niacin in well-closed containers.

CATEGORY—Vitamin B-complex component.

USUAL DOSE—Oral—requirement, **20 mg.** daily; oral and parenteral—therapeutic, **50 mg.** three to ten times a day.

Niacin Injection

Niacin Injection is a sterile solution of niacin, in water for injection, made with the aid of sodium carbonate or sodium hydroxide. It contains not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_6H_5NO_2$.

Identification—To a volume of Niacin Injection, equivalent to about 100 mg. of niacin, add 0.3 ml. of diluted hydrochloric acid, evaporate on a steam bath to about 2 ml., and allow to stand for 1 hour in a cool place. Filter by suction, wash with small volumes of ice-cold water until the last washing does not give a reaction for chloride, and dry at 105° for 1 hour: the niacin so obtained melts at about 235°, page 814, and responds to the *Identification tests*, and meets the requirements for *Ultraviolet absorption* under *Niacin*, page 475.

pH, page 824—The pH of Niacin Injection is between 4.0 and 6.0.

Other requirements—Niacin Injection meets the requirements under *Injections*, page 810.

Assay—Proceed as directed under *Niacin or Niacinamide Assay, Chemical Method*, page 818, using *Standard Niacin Preparation* as the *Standard Preparation* in the *Assay Procedure*, and the following as the *Sample Preparation:* Dilute an accurately measured volume of Niacin Injection, equivalent to about 50 mg. of niacin, with water to 500 ml., in a volumetric flask, and mix. Pipet 10.0 ml. of the solution into a 200-ml. volumetric flask, add water to volume, and mix.

Calculate the quantity, in mg., of $C_6H_5NO_2$ in each ml. of the Injection taken by the formula $(50/V) \times (A_U/A_S)$, in which V is the volume, in ml., of Injection taken.

Packaging and storage—Preserve Niacin Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injection available—Niacin Injection usually available contains the following amounts of niacin: 50 mg. in 1 ml. and 100 mg. in 1 ml.

CATEGORY and DOSE—See Niacin.

Niacin Tablets

Niacin Tablets contain not less than 95.0 percent and not more than 115.0 percent of the labeled amount of $C_6H_5NO_2$.

Identification—Heat on a steam bath a quantity of finely powdered Niacin Tablets, equivalent to about 500 mg. of niacin, with 25 ml. of alcohol for a few minutes, filter, and wash the residue with a few ml. of hot alcohol. To the filtrate add 30 ml. of water, and evaporate on the steam bath to about 25 ml. Cool, filter if insoluble matter separates, and evaporate the filtrate to about 10 ml. Cool, and place in a refrigerator for 1 hour. Filter the separated niacin with suction, wash it with a few ml. of cold alcohol, and dry at 105° for 1 hour: the niacin so obtained melts between 234° and 237°, page 814, and responds to the *Identification tests,* and meets the requirements for *Ultraviolet absorption* under *Niacin,* page 475.

Disintegration, page 878—The disintegration time limit for Niacin Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Niacin Tablets meet the requirements of the content uniformity test for tablets.

Assay—Proceed as directed under *Niacin or Niacinamide Assay, Chemical Method,* page 818, using *Standard Niacin Preparation* as the *Standard Preparation* in the *Assay Procedure,* and the following as the *Sample Preparation:* Weigh and finely powder not less than 20 Niacin Tablets. Weigh accurately a portion of the powder, equivalent to about 25 mg. of niacin, and transfer it with the aid of about 50 ml. of water to a 250-ml. volumetric flask. Heat, if necessary, until no more dissolves, cool, dilute to volume with water and mix. Pipet 10.0 ml. of the solution into a 200-ml. volumetric flask, dilute to volume with water, and mix.

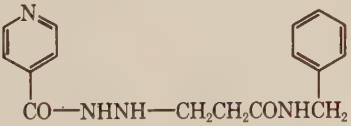
Calculate the quantity, in mg., of $C_6H_5NO_2$ in the portion of the Tablets taken by the formula $25 \times (A_U/A_S)$.

Packaging and storage—Preserve Niacin Tablets in well-closed containers.

Tablets available—Niacin Tablets usually available contain the following amounts of niacin: 25, 50, and 100 mg.

CATEGORY and DOSE—See Niacin.

Nialamide*



Isonicotinic Acid 2-[2-(Benzylcarbamoyl)ethyl]hydrazide

$C_{16}H_{18}N_4O_2$ Mol. wt. 298.35

Nialamide contains not less than 98.0 percent and not more than 101.0 percent $C_{16}H_{18}N_4O_2$, calculated on the dried basis.

Description—Nialamide occurs as a white, practically odorless, crystalline powder.

Solubility—Nialamide is soluble in alcohol and sparingly soluble in water.

Melting range, *Class Ia,* page 815—Nialamide melts between 151° and 155°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Nialamide, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Nialamide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 33,000 solution of Nialamide in alcohol exhibits maxima and minima at the same wavelengths as that of NF Nialamide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 262 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Nialamide at 105° for 3 hours: it loses not more than 1.5 percent of its weight.

Residue on ignition, page 858—Nialamide yields not more than 0.4 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Nialamide is 25 parts per million.

Assay—

Standard preparation—Transfer about 50 mg. of NF Nialamide Reference Standard, accurately weighed, to a 250-ml. volumetric flask, add alcohol to volume, and mix.

Assay preparation—Transfer about 50 mg. of Nialamide, accurately weighed, to a 250-ml. volumetric flask, add alcohol to volume, and mix.

Procedure—Transfer 1.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 25-ml. glass-stoppered flasks, and transfer 1.0 ml. of alcohol to a third flask to serve as the blank. To each flask add 10.0 ml. of acetone and 0.2 ml. of a 1 in 100 solution of ammonium molybdate in diluted hydrochloric acid. Stopper the flasks, mix by shaking, and allow to stand for 10 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 440 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{16}H_{18}N_4O_2$ in the Nialamide taken by the formula $0.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

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* Patented. See notice, page ii.

Packaging and storage—Preserve Nialamide in tight, light-resistant containers.

Category—Antidepressant.

Usual dose range—Initial, **75** to **100 mg.** daily which may be decreased or increased in increments of **12.5** or **25 mg.** at weekly intervals according to response, then reduce gradually to maintenance level.

Nialamide Tablets

Nialamide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{18}N_4O_2$.

Identification—The ultraviolet absorption spectrum of the *Assay preparation,* obtained from Nialamide Tablets as directed in the *Assay,* further diluted to 30 mcg. per ml., exhibits maxima and minima at the same wavelengths as that of the *Standard preparation,* similarly measured.

Disintegration, page 878—The disintegration time limit for Nialamide Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Nialamide Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Nialamide,* page 477.

Assay preparation—Weigh and finely powder not less than 20 Nialamide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg. of nialamide, to a 250-ml. volumetric flask, add 100 ml. of alcohol, and shake mechanically for 20 minutes. Dilute to volume with alcohol, mix, and filter, discarding the first 20 ml. of filtrate. Transfer 50.0 ml. of the subsequent filtrate to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix.

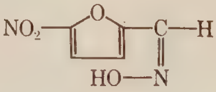
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Nialamide,* page 477. Calculate the quantity, in mg., of $C_{16}H_{18}N_4O_2$ in the portion of the Tablets taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Nialamide Tablets in tight, light-resistant containers.

Tablets available—Nialamide Tablets usually available contain the following amounts of nialamide: 25 and 100 mg.

Category and Dose—See Nialamide.

Nifuroxime



(*Z*)-5-Nitro-2-furaldehyde Oxime

$C_5H_4N_2O_4$ Mol. wt. 156.10

Nifuroxime, dried at 55° for 2 hours, contains not less than 97.0 percent and not more than 103.0 percent of $C_5H_4N_2O_4$.

Caution: Do not use if darker than a medium tan.

Note: Nifuroxime will discolor upon contact with alkaline material and upon exposure to direct sunlight. Do not permit contact with metals other than stainless steel or aluminum.

Description—Nifuroxime occurs as a white to pale yellow, crystalline powder when fresh. Upon standing it may become tan in color.

Solubility—Nifuroxime is slightly soluble in water and is soluble in alcohol. It is very soluble in dimethylformamide.

Identification—To about 50 mg. of Nifuroxime add 5 ml. of water and 5 ml. of sodium hydroxide T.S.: an orange-red colored solution is formed.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Nifuroxime, previously dried at 55° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Nifuroxime Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Nifuroxime in water exhibits maxima and minima at the same wavelengths as that of NF Nifuroxime Reference Standard, similarly measured.

Loss on drying, page 814—Dry Nifuroxime at 55° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Nifuroxime yields not more than 0.1 percent of residue on ignition.

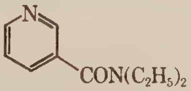
Assay—Dissolve about 100 mg. of Nifuroxime, previously dried at 55° for 2 hours and accurately weighed, in 20 ml. of dimethylformamide in a 1000-ml. volumetric flask, dilute to volume with water, and mix. Transfer 10.0 ml. of the solution to a 100-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Nifuroxime Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 341 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_5H_4N_2O_4$ in the Nifuroxime taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Nifuroxime in tight, light-resistant containers and avoid exposure to direct sunlight.

CATEGORY—Local anti-infective, local antitrichomonal.

Nifuroxime and Furazolidone Powder, page 323
Nifuroxime and Furazolidone Suppositories, page 324

Nikethamide



N,N-Diethylnicotinamide

$C_{10}H_{14}N_2O$ Mol. wt. 178.24

Nikethamide contains not less than 99.0 percent and not more than 101.0 percent of $C_{10}H_{14}N_2O$, calculated on the anhydrous basis.

Description—Nikethamide occurs as a clear, colorless to pale yellowish, somewhat viscous liquid, which crystallizes on standing in the cold and melts again as the temperature rises. It has a faint, characteristic, aromatic odor and a peculiar, bitter taste. Its solutions are clear and nearly colorless, and have not more than a faint odor of diethylamine.

Solubility—Nikethamide is miscible with water, with alcohol, and with ether.

Identification—

A: Dissolve about 3 ml. of Nikethamide in 4 ml. of sodium hydroxide solution (1 in 10) in a suitable flask, and warm on a steam bath for several minutes: diethylamine, recognizable by its odor is evolved. Cool, acidify with 8 ml. of hydrochloric acid, and reflux the mixture for one hour. Cool, and place the reaction flask in an ice bath, then add, carefully and portionwise, sodium hydroxide solution (30 in 100) until the mixture has a pH of 5 to 6, and then adjust the pH to about 3 by the addition of 6 *N* hydrochloric acid: a white precipitate forms. Filter, wash the precipitate with small volumes of cold water, and dry. Triturate a portion of the niacin so obtained with twice its weight of 2,4-dinitrochlorobenzene. Gently heat about 10 mg. of the mixture in a test tube until melted, and continue the heating for a few seconds longer. Cool, and add 3 ml. of alcoholic potassium hydroxide T.S.: a deep red to deep wine-red color is produced.

B: A portion of the niacin obtained in *Identification test A*, when recrystallized from hot water and dried at 105° for 1 hour, melts between 234° and 237°, page 814.

C: To 5 ml. of a solution of Nikethamide (1 in 10) add 5 ml. of cupric sulfate T.S. and 5 ml. of potassium thiocyanate solution (1 in 10), and shake: a flocculent, light green precipitate forms.

Specific gravity, page 866—The specific gravity of Nikethamide is not less than 1.058 and not more than 1.066.

Congealing range, page 794—The congealing range of Nikethamide is between 22° and 24°.

Refractive index, page 858—The refractive index of Nikethamide is not less than 1.522 and not more than 1.524 at 25°.

pH, page 824—The pH of a solution of Nikethamide (1 in 4) is between 6.5 and 7.5.

Residue on ignition, page 858—Nikethamide yields not more than 0.05 percent of residue on ignition.

Chloride, page 784—One g. of Nikethamide shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (70 parts per million).

Diethylamine—To 10 ml. of a solution of Nikethamide (1 in 10) add 0.1 ml. of 0.1 *N* hydrochloric acid and 5 drops of methyl red T.S.: a red color is produced.

Readily oxidizable substances—To 5 ml. of a solution of Nikethamide (1 in 4) add 0.05 ml. of 0.1 *N* potassium permanganate: the pink color is not discharged within 2 minutes.

Other organic impurities—Dissolve 1 ml. of Nikethamide in a mixture of 3 ml. of diluted hydrochloric acid and 6 ml. of water, and heat on a steam bath for 1 hour. Cool, and make distinctly alkaline with sodium hydroxide T.S.: no distinct yellow color is produced.

Water, page 900—Determine the water content of Nikethamide by the titrimetric method: not more than 0.5 percent is found.

Assay—Dissolve 350 mg. of Nikethamide, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 17.82 mg. of $C_{10}H_{14}N_2O$.

Packaging and storage—Preserve Nikethamide in tight containers.

CATEGORY—Central and respiratory stimulant.

USUAL DOSE RANGE—Intramuscular and intravenous, **375 mg.** to **3.75 g.** repeated as needed.

Nikethamide Injection

Nikethamide Injection is a sterile solution of nikethamide in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{14}N_2O$.

Identification—

A: To a portion of Nikethamide Injection, equivalent to about 1.3 g. of nikethamide, add 0.5 ml. of sodium hydroxide solution (30 in 100), and heat on a steam bath: diethylamine, recognizable by its odor, is evolved. Cool, add 8 ml. of hydrochloric acid, and reflux for 1 hour. Cool, and place the reaction flask in an ice bath, then add, carefully and portionwise, sodium hydroxide solution (30 in 100) until the mixture has a pH of 5 to 6, and then adjust the pH to about 3 by the addition of 6 *N* hydrochloric acid: a white precipitate is formed. Filter, wash with small portions of cold water, and dry. A portion of the niacin so obtained responds to *Identification test A* under *Nikethamide*, page 479.

B: A portion of the niacin obtained in *Identification test A*, when recrystallized from hot water and dried at 105° for 1 hour, melts between 234° and 237°, page 814.

Other requirements—Nikethamide Injection meets the requirements under *Injections*, page 810.

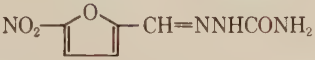
Assay—Dilute an accurately measured volume of Nikethamide Injection, equivalent to about 500 mg. of nikethamide, to 50.0 ml. and mix. Transfer an accurately measured aliquot of the dilution, equivalent to about 50 mg. of nikethamide, to a small round-bottom flask, and add water, if necessary, to make about 5 ml. Add 1 ml. of sulfuric acid, heat gently until most of the water has been expelled, and then continue the heating for 15 minutes. Cool, and transfer the solution with the aid of 20 ml. of water to a distillation flask connected by means of a distillation trap to a well-cooled condenser which dips into approximately 20 ml. of boric acid solution (1 in 25). To the distillation flask add 50 ml. of sodium hydroxide solution (1 in 10), and heat until about 50 ml. of distillate is collected. To the solution in the receiver add 3 drops of methyl red T.S., and titrate the diethylamine so obtained with 0.02 *N* sulfuric acid to a pink end-point. Each ml. of 0.02 *N* sulfuric acid is equivalent to 3.565 mg. of $C_{10}H_{14}N_2O$.

Packaging and storage—Preserve Nikethamide Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injections available—Nikethamide Injection usually available contains the following amounts of nikethamide: 375 mg. in 1.5 ml.; 1.25 g. in 5 ml.; 5 g. in 20 ml.

CATEGORY and DOSE—See Nikethamide.

Nitrofurazone



5-Nitro-2-furaldehyde Semicarbazone

$C_6H_6N_4O_4$ Mol. wt. 198.14

Nitrofurazone, dried at 105° for 1 hour, contains not less than 98.0 percent and not more than 102.0 percent of $C_6H_6N_4O_4$.

Description—Nitrofurazone occurs as an odorless, lemon-yellow, crystalline powder. It darkens slowly on exposure to light. It melts at about 236° with decomposition.

Solubility—Nitrofurazone is soluble in dimethylformamide and is slightly soluble in propylene glycol. It is very slightly soluble in alcohol and in water. It is slightly soluble in polyethylene glycol mixtures. It is practically insoluble in chloroform and in ether.

Identification—Dissolve 400 mg. of potassium hydroxide in a mixture of 9.5 ml. of alcohol and 0.5 ml. of methanol. Immediately before use dilute this solution to 100 ml. with dimethylformamide. To 10 ml. of the prepared solution add a few crystals of Nitrofurazone: a purple solution results.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Nitrofurazone, previously dried at 105° for 1 hour, exhibits maxima only at the same wavelengths as that of NF Nitrofurazone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Nitrofurazone prepared as directed for the *Assay* exhibits an absorbance maximum at 375 ± 2 mμ and an absorbance minimum at 306 ± 2 mμ. The ratio A_{306}/A_{375} does not exceed 0.25.

pH, page 824—Suspend 1 g. of Nitrofurazone in 100 ml. of water, shake the mixture for 15 minutes, allow the suspension to settle, and filter: the pH of the filtrate is between 5.0 and 7.5.

Loss on drying, page 814—Dry Nitrofurazone at 105° for 1 hour: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Nitrofurazone yields not more than 0.05 percent of residue on ignition.

Limit of 5-nitro-2-furfuraldazine—

Standard preparation—Weigh accurately 50.0 mg. of NF 5-Nitro-2-furfuraldazine Reference Standard, previously dried at 105° for 1 hour, and transfer to a 100-ml. volumetric flask. Dissolve in dimethylformamide, dilute to volume with dimethylformamide, and mix. Transfer 5.0 ml. of this solution to a 25-ml. volumetric flask, add 10 ml. of dimethylformamide, dilute to volume with acetone, and mix.

Test preparation—Weigh accurately 2.000 g. of Nitrofurazone, and transfer to a 100-ml. volumetric flask. Dissolve in 60 ml. of dimethylformamide, dilute to volume with acetone, and mix.

Procedure—Apply 5 μl. each of the *Standard preparation* and of the *Test preparation* to a suitable thin-layer chromatographic plate (see page 791) coated with a 0.5-mm. layer of silica gel G. Develop the chromatogram in a solvent system consisting of benzene and acetone (8:2) until the solvent has moved about 10 cm. from the origin. Scan the spot produced by the *Standard preparation* and any spot from the *Test preparation,* having the same R_f as that produced by the *Standard preparation,* with a suitable densitometer equipped with a filter having its maximum transmittance at about 360 mμ. The area and intensity of any spot from the *Test preparation* are not greater than the area and intensity produced by the *Standard* spot (0.5 percent).

Assay—Transfer about 100 mg. of Nitrofurazone, previously dried at 105° for 1 hour and accurately weighed, to a 200-ml. volumetric flask, dissolve in 50 ml. of dimethylformamide, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Nitrofurazone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 375 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_6H_6N_4O_4$ in the Nitrofurazone taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the

Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Nitrofurazone in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat.

CATEGORY—Local anti-infective.

APPLICATION—Topically in various dosage forms in strengths ranging from 0.02 percent to 1 percent.

Nitrofurazone Cream*

Nitrofurazone Cream is nitrofurazone in a suitable, emulsified, water-miscible base. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_6N_4O_4$.

Caution: Avoid exposure at all times to direct sunlight, excessive heat, strong fluorescent lighting, and alkaline materials.

Description—Nitrofurazone Cream is a yellow, opaque, water-miscible cream.

Identification—Dissolve 400 mg. of potassium hydroxide in a mixture of 9.5 ml. of alcohol and 0.5 ml. of methanol. Immediately before use, dilute to 100 ml. with dimethylformamide. To 10 ml. of this solution add an amount of Nitrofurazone Cream, equivalent to about 10 mcg. of nitrofurazone, and mix: a purple color is produced.

Weight variation, page 901—Nitrofurazone Cream meets the requirements of the weight variation test for creams.

Assay—[NOTE: Protect all solutions from light.] Transfer to a 100-ml. beaker an accurately weighed amount of Nitrofurazone Cream, equivalent to about 4 mg. of nitrofurazone, slurry with 25 ml. of chloroform, and then transfer quantitatively to a 100-ml. volumetric flask with the aid of dimethylformamide. Dilute to volume with dimethylformamide, and mix. Transfer 15.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with dimethylformamide, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Nitrofurazone Reference Standard, in the same medium at a concentration of about 6 mcg. per ml., in 1-cm. cells, at the maximum at about 385 mμ, with a suitable spectrophotometer, using dimethylformamide containing 4 ml. of chloroform per 100 ml. as the blank. Calculate the quantity, in mg., of $C_6H_6N_4O_4$ in the portion of Cream taken by the formula $0.667C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Nitrofurazone Cream in tight, light-resistant containers. Avoid exposure to direct sunlight, strong fluorescent lighting, and to excessive heat.

Cream available—Nitrofurazone Cream usually available contains 0.2 percent of nitrofurazone.

CATEGORY and APPLICATION—See Nitrofurazone.

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* Patented. See notice, page ii.

Nitrofurazone Ointment

Nitrofurazone Ointment is nitrofurazone in a suitable water-miscible base. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_6N_4O_4$.

Caution: Avoid exposure at all times to direct sunlight, excessive heat, strong fluorescent lighting, and alkaline materials.

Description—Nitrofurazone Ointment is yellow, opaque, water-miscible, and of ointment-like consistency.

Completeness of solution—One g. of Nitrofurazone Ointment dissolves in 9 ml. of water to form a clear solution.

Identification—Dissolve 400 mg. of potassium hydroxide in a mixture of 9.5 ml. of alcohol and 0.5 ml. of methanol. Immediately before use dilute this solution to 100 ml. with dimethylformamide. To 10 ml. of the prepared solution add an amount of Nitrofurazone Ointment, equivalent to about 10 mcg. of nitrofurazone: a purple solution results.

Assay—

Chromatographic column—Pack a pledget of fine glass wool at the base of a standard 20 × 220-mm. chromatographic tube. Add chromatographic alumina (pH between 9.5 and 10) to the tube to a height of about 80 mm., and pack carefully to avoid air pockets or channels. Wash the column so prepared with 30 ml. of dehydrated alcohol, and discard the washings. Do not allow the column to run dry.

[Note: Protect all solutions from light.]

Standard preparation—Transfer to a 250-ml. volumetric flask about 100 mg. of NF Nitrofurazone Reference Standard, previously dried at 100° for one hour and accurately weighed, dissolve it in 50 ml. of dimethylformamide, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 200-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer to a small beaker an accurately weighed amount of Nitrofurazone Ointment, equivalent to about 4 mg. of nitrofurazone, and dissolve in about 30 ml. of warm dehydrated alcohol (not above 50°). With the aid of dehydrated alcohol, quantitatively transfer the clear, yellow solution to a 100-ml. volumetric flask, dilute to volume with dehydrated alcohol, and mix.

Procedure—Add 25.0 ml. of the *Assay preparation* to the top of the column, then after almost all the solution has passed into the column, wash the column with 40 ml. of dehydrated alcohol, maintaining the liquid level above the adsorbent column throughout the wash. Discard the washings. Pass 70 ml. of water through the column to elute the nitrofurazone. Dilute the eluate to 100.0 ml. with water, mix, centrifuge for 15 minutes, and filter through a medium-porosity, sintered-glass filter, discarding the first 20 ml. of filtrate. Concomitantly determine the absorbance of the solution from the *Assay preparation* (A_U) and of the *Standard preparation* (A_S) in 1-cm. cells with a suitable spectrophotometer at the maximum at about 375 mμ, using water as the blank. Calculate the quantity, in mg., of $C_6H_6N_4O_4$ in the portion of the Ointment taken by the formula $0.4C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Nitrofurazone Ointment in tight, light-resistant containers. Avoid exposure to direct sunlight, strong fluorescent lighting, and to excessive heat.

Ointment available—Nitrofurazone Ointment usually available contains 0.2 percent of nitrofurazone.

Category—See Nitrofurazone.

Nitrofurazone Solution

Nitrofurazone Solution contains not less than 95.0 percent and not more than 105.0 percent (w/w) of the labeled amount of $C_6H_6N_4O_4$.

Caution: Avoid exposure at all times to direct sunlight, excessive heat, and alkaline materials.

Description—Nitrofurazone Solution is a light yellow, clear, somewhat viscous liquid, having a faint characteristic odor.

Solubility—Nitrofurazone Solution is miscible with water.

Identification—Dissolve 400 mg. of potassium hydroxide in a mixture of 9.5 ml. of alcohol and 0.5 ml. of methanol. Immediately before use dilute this solution to 100 ml. with dimethylformamide. To 10 ml. of the prepared solution add 1 drop of Nitrofurazone Solution: a purple solution results.

Assay—

Chromatographic column—Prepare as directed in the *Assay* under *Nitrofurazone Ointment*, page 482.

[Note: Protect all solutions from light.]

Standard preparation—Prepare as directed in the *Assay* under *Nitrofurazone Ointment*, page 482.

Assay preparation—Transfer to a small beaker an accurately weighed amount of Nitrofurazone Solution, equivalent to about 4 mg. of nitrofurazone, and mix with about 30 ml. of dehydrated alcohol. Quantitatively transfer the clear, yellow solution to a 100-ml. volumetric flask, dilute to volume with dehydrated alcohol, and mix.

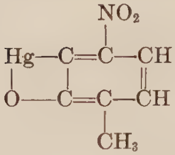
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Nitrofurazone Ointment*, page 482. Calculate the quantity, in mg., of $C_6H_6N_4O_4$ in the portion of the Solution taken by the formula $0.4C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Nitrofurazone Solution in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat.

Solution available—Nitrofurazone Solution usually available contains 0.2 percent (w/w) of nitrofurazone.

Category—See Nitrofurazone.

Nitromersol



5-Methyl-2-nitro-7-oxa-8-mercurabicyclo[4.2.0]octa-1,3,5-triene

$C_7H_5HgNO_3$ Mol. wt. 351.71

Nitromersol, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_7H_5HgNO_3$.

Description—Nitromersol occurs as brownish yellow to yellow granules or as a brownish yellow to yellow powder. It is odorless and tasteless.

Solubility—Nitromersol dissolves in solutions of alkalies and of ammonia by opening of the anhydride ring and the formation of a salt. It is insoluble in water, and is almost insoluble in alcohol, in acetone, and in ether.

Identification—

A: A solution of Nitromersol (1 in 1000) in sodium hydroxide T.S. possesses a reddish orange color. The addition of diluted hydrochloric acid to this solution causes the color to disappear and a yellowish, flocculent precipitate to form.

B: To 20 ml. of a solution of Nitromersol, made by dissolving 250 mg. of Nitromersol in 2.5 ml. of sodium hydroxide T.S. and diluting to 20 ml., add about 3 ml. of diluted hydrochloric acid: a yellowish precipitate forms. Upon filtration, the filtrate is nearly colorless or slightly yellow. Retain the filtrate for the test for *Mercury ions*. Dissolve the precipitate in 20 ml. of water to which 2.5 ml. of sodium hydroxide T.S. has been added, add 500 mg. of sodium hydrosulfite, and heat to boiling: a heavy deposit of metallic mercury forms.

Loss on drying, page 814—Dry Nitromersol at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Nitromersol yields not more than 0.1 percent of residue on ignition.

Mercury ions—To the filtrate obtained in *Identification test B*, add an equal volume of hydrogen sulfide T.S.: no darkening in color is produced although a small amount of a flocculent, light yellow precipitate may form.

Alkali-insoluble substances—Add 7 ml. of sodium hydroxide T.S. to 1.0 g. of Nitromersol and then dilute to 20 ml. with water. The resulting solution, upon standing in a glass-stoppered vessel for 24 hours in the dark, shows no more than a slight amount of insoluble material. Collect the insoluble residue, if any, in a tared filter crucible, wash the residue with warm water, and dry at 105° for 1 hour: the weight of the insoluble material does not exceed 0.1 percent.

Uncombined nitrocresol—Shake 500 mg. of Nitromersol with 50 ml. of benzene, filter, evaporate the filtrate to dryness in a tared dish, and dry the residue at 80° for 2 hours: the weight of the residue does not exceed 5 mg. (1 percent).

Assay—Accurately weigh about 200 mg. of Nitromersol, previously ground to a fine powder and dried at 105° for 2 hours, and transfer to a 500-ml. Kjeldahl flask. Add 15 ml. of sulfuric acid, digest over a low flame for 15 to 20 minutes, cool, and add, dropwise, enough 30 percent hydrogen peroxide to decolorize the solution. Digest for 2 or 3 minutes, adding more hydrogen peroxide, if necessary, to produce a colorless solution. Cool, dilute to about 100 ml., and add potassium permanganate T.S. until a permanent pink color persists on heating. Then add hydrogen peroxide T.S., dropwise, until the color is completely discharged. Cool, and add 5 ml. of nitric acid which has been diluted with 10 ml. of water. Add 5 ml. of ferric ammonium sulfate T.S., and titrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* ammonium thiocyanate is equivalent to 17.59 mg. of $C_7H_5HgNO_3$.

Packaging and storage—Preserve Nitromersol in tight containers.

CATEGORY—Local anti-infective.

APPLICATION—Topically as a solution or tincture.

Nitromersol Solution

Nitromersol Solution yields, from each 100 ml., not less than 180.0 mg. and not more than 220.0 mg. of $C_7H_5HgNO_3$.

Nitromersol	2 g.
Sodium Hydroxide	0.4 g.
Monohydrated Sodium Carbonate	4.25 g.
Purified Water, a sufficient quantity,	
To make	1000 ml.

Dissolve the sodium hydroxide and the monohydrated sodium carbonate in 50 ml. of purified water, add the nitromersol and stir until dissolved. Gradually add a sufficient quantity of purified water to make 1000 ml.

Caution: Dilutions of Nitromersol Solution should be prepared as needed since they tend to precipitate upon standing.

Description—Nitromersol Solution is a clear, reddish orange solution. It is affected by light.

Specific gravity, page 866—The specific gravity of Nitromersol Solution is not less than 1.005 and not more than 1.010.

Identification—

A: To 100 ml. of Nitromersol Solution add 3 ml. of diluted hydrochloric acid: a yellowish precipitate forms. Filter and retain both the filtrate and the precipitate.

B: Add the precipitate from *Identification test A* to 20 ml. of water and 2.5 ml. of sodium hydroxide T.S. Add 500 mg. of sodium hydrosulfite and heat to boiling: a heavy deposit of metallic mercury is formed.

Mercury ions—To the filtrate obtained in *Identification test A* add an equal volume of hydrogen sulfide T.S.: no darkening in color is produced, although a small amount of a flocculent, light yellow precipitate may form.

Assay—Transfer 50.0 ml. of Nitromersol Solution to a 500-ml. Kjeldahl flask, add a few glass beads and evaporate to about 5 ml. Continue as directed in the *Assay* under *Nitromersol,* page 484, beginning with "Add 15 ml of sulfuric acid . . . ."

Packaging and storage—Preserve Nitromersol Solution in tight, light-resistant containers.

Category—See Nitromersol.

Nitromersol Tincture

Nitromersol Tincture yields, from each 100 ml., not less than 450.0 mg. and not more than 550.0 mg. of $C_7H_5HgNO_3$.

Nitromersol	5 g.
Sodium Hydroxide	1 g.
Acetone	100 ml.
Alcohol	525 ml.
Purified Water, a sufficient quantity,	
To make	1000 ml.

Dissolve the nitromersol in a mixture of the acetone, alcohol, and the sodium hydroxide dissolved in 50 ml. of purified water and finally add a sufficient quantity of purified water to make the product measure 1000 ml.

Note: Nitromersol Tincture may be colored by the addition of any suitable color or combination of colors certified by the federal Food and Drug Administration for use in drugs.

Description—Nitromersol Tincture is a clear liquid with the characteristic odor of acetone and of alcohol. It is affected by light.

Specific gravity, page 866—The specific gravity of Nitromersol Tincture is not less than 0.905 and not more than 0.915.

Identification—Acidify 100 ml. of Nitromersol Tincture with diluted hydrochloric acid, evaporate to about 15 ml., and filter. The nitromersol so obtained responds to *Identification tests A* and *B* under *Nitromersol,* page 484.

Assay—Pipet 25.0 ml. of Nitromersol Tincture into a 500-ml. Kjeldahl flask, add a few glass beads and evaporate to about 5 ml. Continue as directed in the *Assay* under *Nitromersol,* page 484, beginning with "Add 15 ml. of sulfuric acid . . . ."

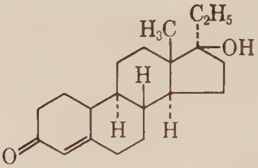
Alcohol content—Determine the alcohol content by the gas-liquid chromatographic procedure, page 772, using methyl ethyl ketone as the internal standard. Nitromersol Tincture contains from 47 to 53 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Nitromersol Tincture in tight, light-resistant containers.

Category—See Nitromersol.

Nondestearinated Cod Liver Oil, page 183

Norethandrolone*



17-Hydroxy-19-nor-17α-pregn-4-en-3-one

$C_{20}H_{30}O_2$ Mol. wt. 302.46

Norethandrolone contains not less than 96.0 percent and not more than 102.0 percent of $C_{20}H_{30}O_2$, calculated on the dried basis.

Description—Norethandrolone occurs as a white, odorless, crystalline powder. It is stable in air, but darkens slightly under prolonged exposure to light.

Solubility—Norethandrolone is practically insoluble in water, sparingly soluble in ether, freely soluble in alcohol and in acetone, and very soluble in chloroform.

Identification—Prepare a solution of Norethandrolone in chloroform containing 500 mcg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution and 10 μl. of a chloroform solution of NF Norethandrolone Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of methanol and chloroform (1:19) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Melting range, page 814—Norethandrolone melts between 130° and 136°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Norethandrolone, previously dried at 60° in vacuum for 3 hours, exhibits maxima only at the same wavelengths as that of NF Norethandrolone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Norethandrolone in methanol exhibits maxima and minima at the same wavelengths as that of NF Norethandrolone Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 241 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Norethandrolone, calculated on the dried basis, determined in a solution in methanol containing 200 mg. of Norethandrolone in each 10 ml., is between +19° and +22°.

Loss on drying, page 814—Dry Norethandrolone at 60° in vacuum for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Norethandrolone yields not more than 0.2 percent of residue on ignition.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Norethandrolone Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Norethandrolone, previously dried at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of chloroform and methanol (95:15), and determining the absorbance at the maximum at about 241 mμ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Norethandrolone taken: not more than 3 percent is found.

Assay—

Standard preparation—Dissolve in chloroform a suitable quantity of NF Norethandrolone Reference Standard, previously dried at 60° in vacuum for 3 hours and accurately weighed, and dilute quantitatively and stepwise with chloroform to obtain a solution having a concentration of about 40 mcg. per ml., and mix. Pipet 5.0 ml. of this solution into a glass-stoppered 50-ml. conical flask.

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* Patented. See notice, page ii.

Assay preparation—Weigh accurately about 100 mg. of Norethandrolone, dissolve in sufficient chloroform to make 200.0 ml., and mix. Pipet 20.0 ml. of this solution into a 250-ml. volumetric flask, add chloroform to volume, and mix. Pipet 5.0 ml. of the resulting solution into a glass-stoppered, 50-ml. conical flask.

Procedure—To each of the flasks containing the *Assay preparation* and the *Standard preparation*, and to a similar flask containing 5.0 ml. of chloroform to serve as the blank, add 10.0 ml. of a solution of 375 mg. of isoniazid and 0.47 ml. of hydrochloric acid in 500 ml. of methanol. Mix, and allow to stand for 60 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 380 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{20}H_{30}O_2$ in the portion of Norethandrolone taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Norethandrolone in well-closed, light-resistant containers.

Category—Androgen.

Usual dose—**10 mg.** two or three times a day.

Norethandrolone Tablets

Norethandrolone Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{20}H_{30}O_2$.

Identification—Triturate a number of Norethandrolone Tablets, equivalent to about 50 mg. of norethandrolone, with 15 ml. of chloroform, filter, evaporate the filtrate to dryness on a steam bath, and dry at 105° for 3 hours: the residue so obtained meets the requirements for *Infrared absorption* under *Norethandrolone,* page 486.

Disintegration, page 878—The disintegration time limit for Norethandrolone Tablets is 15 minutes.

Content uniformity, *Method I*, page 799—Norethandrolone Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Norethandrolone,* page 486.

Assay preparation—Weigh and finely powder not less than 20 Norethandrolone Tablets. Weigh accurately a portion of the powder, equivalent to about 40 mg. of norethandrolone, and transfer to a separator with the aid of 15 ml. of water. Extract with four 25-ml. portions of chloroform, filtering each portion through chloroform-washed cotton into a 200-ml. volumetric flask. Dilute to volume with chloroform, and mix. Transfer 20.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Pipet 5.0 ml. of the resulting solution into a glass-stoppered, 50 ml. conical flask.

Procedure—Proceed as directed in the *Assay* under *Norethandrolone*, page 486. Calculate the quantity, in mg., of $C_{20}H_{30}O_2$ in the portion of the Tablets taken by the formula $C \times (A_U/A_S)$.

Packaging and storage—Preserve Norethandrolone Tablets in well-closed, light-resistant containers.

Tablets available—Norethandrolone Tablets usually available contain the following amount of norethandrolone: 10 mg.

Category and Dose—See Norethandrolone.

Norethindrone Tablets

Norethindrone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{26}O_2$.

Identification—Mix an amount of powdered Norethindrone Tablets, equivalent to about 50 mg. of norethindrone, with 15 ml. of solvent hexane, and stir occasionally for 15 minutes. Centrifuge the mixture, then decant and discard the solvent hexane. Extract the residue with two additional 10-ml. portions of solvent hexane, centrifuging and decanting as before, and discard the solvent hexane.

Add 25 ml. of chloroform to the residue, mix by shaking for 1 to 2 minutes, and filter. Evaporate the filtrate to about 3 ml., add a few ml. of solvent hexane to induce crystallization, and evaporate to dryness: the infrared absorption spectrum of a potassium bromide dispersion prepared from the residue so obtained exhibits maxima only at the same wavelengths as that of USP Norethindrone Reference Standard, crystallized from the same solvent and similarly measured.

Disintegration, page 878—The disintegration time limit for Norethindrone Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Norethindrone Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered Tablet to a 100-ml. volumetric flask with the aid of about 75 ml. of alcohol. Heat the alcohol to boiling, and allow to remain at a temperature just below the boiling point for about 15 minutes with occasional swirling. Cool to room temperature, dilute to volume with alcohol, and mix. Centrifuge a portion of the mixture at about 2000 r.p.m. until the solution becomes clear. Dilute a portion of the supernatant liquid quantitatively and stepwise, if necessary, with alcohol to provide a solution containing approximately 10 mcg. of norethindrone per ml. Concomitantly determine the absorbance of this solution and of a solution of USP Norethindrone Reference Standard, in alcohol, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 240 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{20}H_{26}O_2$ in the Tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of norethindrone in the tablet; D is the exact concentration, in mcg. per ml., of norethindrone in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Norethindrone Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of norethindrone, to a separator, add 10 ml. of water, and extract with three 25-ml. portions of chloroform, filtering each extract through chloroform-washed cotton. Evaporate the combined chloroform extracts to dryness on a steam bath, reducing the application of heat as dryness is approached. Dissolve the residue in alcohol, transfer to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Transfer 5.0 ml. of the solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of USP Norethindrone Reference Standard, in alcohol at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 240 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{20}H_{26}O_2$ in the portion of the Tablets taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

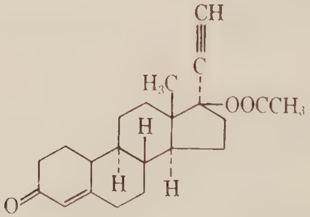
Packaging and storage—Preserve Norethindrone Tablets in well-closed containers.

Tablets available—Norethindrone Tablets usually available contain the following amount of norethindrone: 5 mg.

CATEGORY—Progestin.

USUAL DOSE RANGE OF NORETHINDRONE —**5** to **30 mg.** daily.

Norethindrone Acetate*



17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one Acetate

$C_{22}H_{28}O_3$ Mol. wt. 340.47

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* Patented. See notice, page ii.

Norethindrone Acetate contains not less than 97.0 percent and not more than 103.0 percent of $C_{22}H_{28}O_3$, calculated on the dried basis.

Description—Norethindrone Acetate occurs as a white to creamy white, odorless, crystalline powder.

Solubility—Norethindrone Acetate is practically insoluble in water. It is soluble in ether and in alcohol, very soluble in chloroform, and freely soluble in dioxane.

Completeness of solution—The solution prepared for the determination of *Specific rotation* is clear and free from undissolved solids.

Melting range, *Class Ia,* page 815—Norethindrone Acetate melts between 158° and 164°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Norethindrone Acetate, previously dried in vacuum at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Norethindrone Acetate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Norethindrone Acetate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Norethindrone Acetate Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Norethindrone Acetate, calculated on the dried basis, determined in a solution in dioxane containing 200 mg. in each 10 ml., is between $-32°$ and $-38°$.

Loss on drying, page 814—Dry Norethindrone Acetate in vacuum at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Foreign steroids and other impurities—*Standard preparation*—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Norethindrone Acetate Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Norethindrone Acetate previously dried in vacuum at 105° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of benzene and ethyl acetate (1:1) and determining the absorbance at the maximum at about 240 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Norethindrone Acetate taken: not more than 3 percent is found.

Assay—Transfer about 100 mg. of Norethindrone Acetate, accurately weighed, to a 200-ml. volumetric flask, add alcohol to volume, and mix. Transfer 5.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Norethindrone Acetate Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 240 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{22}H_{28}O_3$ in the Norethindrone Acetate taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Norethindrone Acetate in well-closed containers.

CATEGORY—Progestin.
USUAL DOSE—**10 mg.** daily.
USUAL DOSE RANGE—**5** to **15 mg.**

Norethindrone Acetate Tablets

Norethindrone Acetate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{28}O_3$.

Identification—Powder a number of Norethindrone Acetate Tablets equivalent to about 50 mg. of norethindrone acetate. Add 15 ml. of solvent hexane, and stir occasionally for 15 minutes. Centrifuge the mixture, then decant and discard the solvent hexane. Extract the residue with two additional 10-ml. portions of solvent hexane, centrifuging and decanting as before, and discard the solvent hexane. Add 25 ml. of chloroform to the residue, and mix by shaking for 1 to 2 minutes. Filter, and evaporate the filtrate to about 3 ml. Add a few ml. of solvent hexane to induce crystallization, and evaporate to dryness: the infrared absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima at the same wavelengths as that of NF Norethindrone Acetate Reference Standard, crystallized from the same solvent mixture and similarly measured.

Disintegration, page 878—The disintegration time limit for Norethindrone Acetate Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Norethindrone Acetate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer one finely powdered tablet to a 100-ml. volumetric flask with the aid of about 75 ml. of alcohol. Heat the alcohol to boiling, and allow the mixture to remain at a temperature just below the boiling point for about 15 minutes with occasional swirling. Cool to room temperature, dilute to volume with alcohol, mix, and centrifuge a portion of the contents at about 2000 r.p.m. until the solution becomes clear. Dilute a portion of the supernatant solution quantitatively and stepwise with alcohol to provide a solution containing approximately 10 mcg. of norethindrone acetate per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Norethindrone Acetate Reference Standard in alcohol, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 240 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{22}H_{28}O_3$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of norethindrone acetate in the tablet; D is the exact concentration, in mcg. per ml., of the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

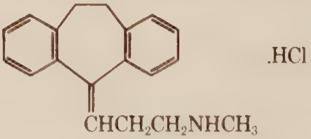
Assay—Weigh and finely powder not less than 20 Norethindrone Acetate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of norethindrone acetate, to a separator, add 10 ml. of water, and extract with three 25-ml. portions of chloroform, filtering each extract through chloroform-washed cotton. Evaporate the combined chloroform extracts to dryness on a steam bath, reducing the application of heat as dryness is approached. Dissolve the residue in alcohol, quantitatively transfer the solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Pipet a 5.0-ml. aliquot into a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Norethindrone Acetate Reference Standard in alcohol, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 240 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{22}H_{28}O_3$ in the portion of the Tablets taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Norethindrone Acetate Tablets in well-closed containers.

Tablets available—Norethindrone Acetate Tablets usually available contain the following amount of norethindrone acetate: 5 mg.

CATEGORY and DOSE—See Norethindrone Acetate.

Nortriptyline Hydrochloride*



10,11-Dihydro-*N*-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine Hydrochloride

$C_{19}H_{21}N.HCl$ Mol. wt. 299.85

Nortriptyline Hydrochloride contains not less than 97.0 percent and not more than 101.5 percent of $C_{19}H_{21}N.HCl$, calculated on the dried basis.

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* Patent pending. See notice, page ii.

Description—Nortriptyline Hydrochloride occurs as a white to off-white powder having a slight, characteristic odor.

Solubility—Nortriptyline Hydrochloride is soluble in chloroform and in water, and sparingly soluble in methanol. It is practically insoluble in ether, in benzene, and in most other organic solvents.

Identification—Nortriptyline Hydrochloride responds to the tests for *Chloride,* page 808, when tested as specified for alkaloidal hydrochlorides.

Melting range, page 814—Nortriptyline Hydrochloride melts within a range of 3° between 215° and 220°.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 20 solution of Nortriptyline Hydrochloride, previously dried at 105° for 3 hours, in chloroform exhibits maxima only at the same wavelengths as that of NF Nortriptyline Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Nortriptyline Hydrochloride in methanol exhibits maxima and minima at the same wavelengths as that of NF Nortriptyline Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 239 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Nortriptyline Hydrochloride at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Heavy metals, *Method II,* page 806—The heavy metals limit for Nortriptyline Hydrochloride is 30 parts per million.

Assay—Dissolve about 600 mg. of Nortriptyline Hydrochloride, accurately weighed, in 50 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 29.98 mg. of $C_{19}H_{21}N.HCl$.

Packaging and storage—Preserve Nortriptyline Hydrochloride in tight, light-resistant containers.

CATEGORY—Antidepressant.

USUAL DOSE RANGE—An amount of Nortriptyline Hydrochloride equivalent to **20** to **100 mg.** of nortriptyline base daily in divided doses.

Nortriptyline Hydrochloride Capsules

Nortriptyline Hydrochloride Capsules contain nortriptyline hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{19}H_{21}N$ (nortriptyline base).

Identification—

A: The solution prepared from Nortriptyline Hydrochloride Capsules as directed in the *Assay* exhibits an absorbance maximum at 239 ± 3 mμ.

B: A filtered solution of Nortriptyline Hydrochloride Capsules, equivalent to nortriptyline hydrochloride solution (1 to 20), responds to the tests for *Chloride,* page 808, when tested as specified for alkaloidal hydrochlorides.

Content uniformity, *Method II,* page 798—Nortriptyline Hydrochloride Capsules meet the requirements of the content uniformity test for capsules, using the following special procedure: Quantitatively transfer the contents of a capsule as completely as possible to a 100-ml. volumetric flask. Rinse the empty capsule with methanol, and add these rinsings to the flask. Add 50 ml. of methanol, and shake mechanically for 15 minutes. Dilute to volume with methanol, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol to provide a solution containing approximately 10 mcg. of nortriptyline base per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Nortriptyline Hydrochloride Reference Standard, in the same medium, at a concentration of about 11.4 mcg. per ml. of nortriptyline hydrochloride, in 1-cm. cells, at the maximum at about 239 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{19}H_{21}N$ in the capsule by the formula $(T/D) \times (0.8784C) \times (A_U/A_S)$, in which T is the labeled quantity of nortriptyline base, in mg., in the capsule; D is the exact concentration, in mcg. per ml., of nortriptyline base in the sample solution, based upon the labeled quantity per capsule and the extent of dilution; 0.8784 is the ratio of the molecular weight of nortriptyline base to that of nortriptyline hydrochloride;

C is the exact concentration of nortriptyline hydrochloride in the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

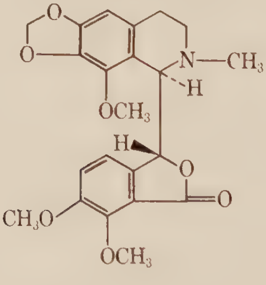
Assay—Transfer as completely as possible the contents of not less than 20 Nortriptyline Hydrochloride Capsules to a suitable tared container, and weigh. Mix the powder thoroughly with a glass rod, and transfer an accurately weighed portion of the powder, equivalent to about 10 mg. of nortriptyline base, to a 125-ml. separator. Add 50 ml. of water, mix, and make the suspension distinctly alkaline (to pH 11 or above as indicated by pH indicator paper) by the dropwise addition of sodium hydroxide solution (1 in 2). Extract the nortriptyline base with four 25-ml. portions of chloroform, filtering each extract into a 250-ml. beaker through about 12 g. of anhydrous sodium sulfate previously washed with 25 ml. of chloroform. Rinse the sodium sulfate with four 5-ml. portions of chloroform, and collect the rinsings in the beaker. Evaporate the combined chloroform solution to about 10 ml. with the aid of heat and a current of air. Quantitatively transfer the contents of the beaker to a 200-ml. volumetric flask with the aid of chloroform. Evaporate the chloroform to dryness with the aid of air alone. [*Caution: Do not use heat.*] Dissolve the residue in 0.1 *N* hydrochloric acid, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Transfer 10.0 ml. of the solution to a 50-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Nortriptyline Hydrochloride Reference Standard in water, at a concentration of about 11.4 mcg. per ml., in 1-cm. cells, at the maximum at about 239 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{19}H_{21}N$ in the portion of the Capsules taken by the formula $0.8784C \times (A_U/A_S)$, in which 0.8784 is the ratio of the molecular weight of nortriptyline base to that of nortriptyline hydrochloride, *C* is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Nortriptyline Hydrochloride Capsules in tight containers.

Capsules available—Nortriptyline Hydrochloride Capsules usually available contain nortriptyline hydrochloride equivalent to the following amounts of nortriptyline base: 10 and 25 mg.

CATEGORY and DOSE—See Nortriptyline Hydrochloride.

Noscapine



(−)-Narcotine

$C_{22}H_{23}NO_7$ Mol. wt. 413.43

Noscapine contains not less than 99.0 percent and not more than 100.5 percent of $C_{22}H_{23}NO_7$, calculated on the anhydrous basis.

Description—Noscapine occurs as a fine, white or practically white, crystalline powder. It is odorless, and stable in the presence of light and air. Its solution in chloroform is levorotatory.

Solubility—Noscapine is practically insoluble in water, freely soluble in chloroform, and soluble in acetone and in benzene. It is slightly soluble in alcohol and in ether.

Identification—

A: Place about 100 mg. of Noscapine in a small porcelain dish, add a few drops of sulfuric acid, and stir: a greenish yellow solution is produced, and on warming it becomes red and then turns violet.

B: Dissolve about 200 mg. of Noscapine in 5 ml. of diluted hydrochloric acid, and add 10 ml. of a saturated solution of sodium acetate: after standing for a short time, the Noscapine is almost completely precipitated.

Melting range, page 814—Noscapine melts between 174° and 176°.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 16,000 solution of Noscapine in methanol exhibits absorption maxima at 290 ± 1 mμ and at 310 ± 1 mμ and a minimum at 263 ± 2 mμ. The ratio A_{310}/A_{290} is about 1.23.

Water, page 900—Determine the water content of Noscapine by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Noscapine yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—A 750-mg. portion of Noscapine shows no more chloride than corresponds to 0.2 ml. of 0.02 *N* hydrochloric acid (0.02 percent).

Morphine—Dissolve 100 mg. of Noscapine in 10 ml. of 0.1 *N* hydrochloric acid. To 1 ml. of this solution add 5 ml. of diluted ferricyanide reagent (prepared by dissolving 500 mg. of potassium ferricyanide in 50 ml. of water, adding 0.5 ml. of ferric chloride T.S. and diluting 5 ml. of the resulting solution to 25 ml.): no blue or dark green color develops within 1 minute.

Assay—Dissolve about 1.5 g. of Noscapine, accurately weighed, in 25 ml. of glacial acetic acid. Add 25 ml. of dioxane and 5 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 41.34 mg. of $C_{22}H_{23}NO_7$.

Packaging and storage—Preserve Noscapine in well-closed containers.

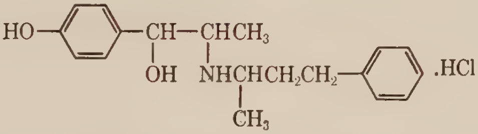
CATEGORY—Antitussive.

USUAL DOSE—**15 mg.** up to four times a day.

USUAL DOSE RANGE—**15 to 30 mg.**

Novobiocin, Calcium, page 124
Novobiocin, Calcium, Oral Suspension, page 124
Novobiocin, Sodium, page 652
Novobiocin, Sodium, Capsules, page 653
Novobiocin, Sodium, for Injection, page 653

Nylidrin Hydrochloride*



p-Hydroxy-α-[1-[(1-methyl-3-phenylpropyl)amino]ethyl]benzyl Alcohol Hydrochloride

$C_{19}H_{25}NO_2 . HCl$ Mol. wt. 335.88

Nylidrin Hydrochloride, dried at 60° in vacuum for 3 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{19}H_{25}NO_2 . HCl$.

Description—Nylidrin Hydrochloride occurs as a white, odorless, practically tasteless, crystalline powder.

Solubility—Nylidrin Hydrochloride is sparingly soluble in water and in alcohol. It is very slightly soluble in chloroform and in ether.

Identification—

A: Dissolve about 100 mg. of Nylidrin Hydrochloride in 10 ml. of water with heating, and cool. To 5 ml. of the solution add 10 drops of a solution of 1-nitroso-2-naphthol in alcohol (1 in 100). Heat to boiling and add 2 drops of nitric acid: a cherry-red color forms (*distinction from epinephrine and ephedrine*).

B: Add 2 drops of nitric acid and 1 ml. of silver nitrate T.S. to the remaining 5 ml. of the Nylidrin Hydrochloride solution prepared in *Identification test A:* a white precipitate forms which is insoluble in diluted nitric acid, but soluble in ammonia T.S. (*presence of chloride*).

C: Dissolve about 500 mg. of Nylidrin Hydrochloride in 20 ml. of warm water, cool, transfer to a 60-ml. separator, and add 1 ml. of sodium hydroxide T.S. Extract the liberated base with two 10-ml.

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* Patented. See notice, page ii.

portions of chloroform. Dry the extract with anhydrous sodium sulfate, allowing the mixture to stand for 10 minutes after an excess of the drying agent has been added. Filter through a dry filter paper, collect the filtrate in a 50-ml. beaker, and evaporate to dryness on a steam bath in a current of warm air. Recrystallize the residue from diluted alcohol and dry the product in a vacuum desiccator over phosphorus pentoxide for 30 minutes: the nylidrin so obtained melts between 109° and 112°, page 814.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Nylidrin Hydrochloride, previously dried in vacuum at 60° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Nylidrin Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 10,000 solution of Nylidrin Hydrochloride in alcohol exhibits maxima and minima at the same wavelengths as that of NF Nylidrin Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 277 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Nylidrin Hydrochloride (1 in 100) is between 4.5 and 6.5.

Loss on drying, page 814—Dry Nylidrin Hydrochloride in vacuum at 60° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Nylidrin Hydrochloride yields not more than 0.5 percent of residue on ignition.

Assay—Weigh accurately about 700 mg. of Nylidrin Hydrochloride, previously dried at 60° in vacuum for 3 hours, and transfer it to a 150-ml. tall form beaker. Add 50 ml. of glacial acetic acid, and heat on a steam bath until solution is complete. Add 10 ml. of mercuric acetate T.S., cool, add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 33.59 mg. of $C_{19}H_{25}NO_2.HCl$.

Packaging and storage—Preserve Nylidrin Hydrochloride in tight containers.

CATEGORY—Peripheral vasodilator.

USUAL DOSE—Oral, **6 mg.** three times a day. Parenteral, **5 mg.** one or more times a day.

USUAL DOSE RANGE—Oral, **3** to **12 mg.** Parenteral, **2.5** to **5 mg.**

Nylidrin Hydrochloride Injection

Nylidrin Hydrochloride Injection is a sterile solution of nylidrin hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{19}H_{25}NO_2.HCl$.

Identification—

A: Transfer a volume of Nylidrin Hydrochloride Injection, equivalent to about 100 mg. of nylidrin hydrochloride, to a 60-ml. separator, and proceed as directed in *Identification test C* under *Nylidrin Hydrochloride,* page 493, beginning with "... add 1 ml. of sodium hydroxide T.S. ..."

B: Nylidrin Hydrochloride Injection responds to *Identification test B* under *Nylidrin Hydrochloride,* page 493.

Other requirements—Nylidrin Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—Transfer to a 125-ml. separator an accurately measured volume of Nylidrin Hydrochloride Injection, equivalent to about 40 mg. of nylidrin hydrochloride, and dilute to 35 ml. with water. Add 5 ml. of sodium carbonate T.S., and extract the solution with four 10-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water, and then extract the wash solution with 5 ml. of chloroform. Filter the combined chloroform extracts through a tightly packed, chloroform-washed pledget of cotton and wash the cotton with 5 ml. of chloroform. Add 3 drops of methanolic methyl red T.S. to the chloroform solution, and titrate with 0.01 *N* perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* perchloric acid is equivalent to 3.359 mg. of $C_{19}H_{25}NO_2.HCl$.

Packaging and storage—Preserve Nylidrin Hydrochloride Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Nylidrin Hydrochloride Injection usually available contains the following amounts of nylidrin hydrochloride: 5 mg. in 1 ml., and 50 mg. in 10 ml.

CATEGORY and DOSE—See Nylidrin Hydrochloride.

Nylidrin Hydrochloride Tablets

Nylidrin Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{19}H_{25}NO_2.HCl$.

Identification—Transfer to a 60-ml. separator an amount of powdered Nylidrin Hydrochloride Tablets, equivalent to about 100 mg. of nylidrin hydrochloride, add 20 ml. of water, and proceed as directed in *Identification test C* under *Nylidrin Hydrochloride,* page 493, beginning with "... add 1 ml. of sodium hydroxide T.S. . . ."

Disintegration, page 878—The disintegration time limit for Nylidrin Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Nylidrin Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask, add tribasic sodium phosphate solution (1 in 50) to volume, mix, and centrifuge a portion of the mixture at high speed. Dilute an accurately measured volume of the supernatant liquid quantitatively and stepwise, if necessary, with the phosphate solution to provide a solution containing approximately 10 mcg. of nylidrin hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Nylidrin Hydrochloride Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 242 mμ, with a suitable spectrophotometer, using the phosphate solution as the blank. Calculate the quantity, in mg., of $C_{19}H_{25}NO_2.HCl$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of nylidrin hydrochloride, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of nylidrin hydrochloride in the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

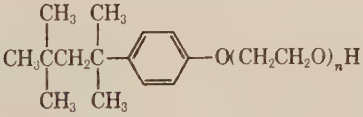
Assay—Weigh and finely powder not less than 20 Nylidrin Hydrochloride Tablets. Transfer to a 125-ml. separator a portion of the powder, accurately weighed, equivalent to about 40 mg. of nylidrin hydrochloride. Add 35 ml. of water and 5 ml. of sodium carbonate T.S., and proceed as directed in the *Assay* under *Nylidrin Hydrochloride Injection,* page 494, beginning with ". . . extract the solution with four 10-ml. portions of chloroform. . . ."

Packaging and storage—Preserve Nylidrin Hydrochloride Tablets in tight containers.

Tablets available—Nylidrin Hydrochloride Tablets usually available contain the following amount of nylidrin hydrochloride: 6 mg.

CATEGORY and DOSE—See Nylidrin Hydrochloride.

Octoxynol



Polyethylene Glycol Mono[*p*-(1,1,3,3-tetramethylbutyl)phenyl] Ether

$C_{34}H_{62}O_{11}$ (av.) Mol. wt. (av.) 647

Octoxynol is an anhydrous liquid mixture of mono[*p*-(1,1,3,3-tetramethylbutyl)phenyl] ethers of polyethylene glycols in which n varies from 5 to 15, and which has an average molecular weight of 647, corresponding to the formula $C_{34}H_{62}O_{11}$.

Description—Octoxynol occurs as a clear, pale yellow, viscous liquid having a faint odor and a bitter taste.

Solubility—Octoxynol is miscible with water, with alcohol, and with acetone. It is soluble in benzene and in toluene, and is practically insoluble in solvent hexane.

Specific gravity, page 866—The specific gravity of Octoxynol is not less than 1.059 and not more than 1.068.

Refractive index, page 858—The refractive index of Octoxynol is about 1.489.

pH, page 824—The pH of a solution of Octoxynol (1 in 20) is between 7.0 and 9.0.

Packaging and storage—Preserve Octoxynol in tight containers.

CATEGORY—Surfactant.

Yellow Ointment

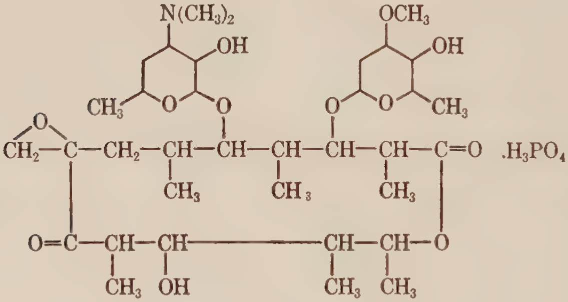
Yellow Wax	**50 g.**
Petrolatum	**950 g.**
To make	**1000 g.**

Melt the yellow wax in a suitable dish on a steam bath, add the petrolatum, warm until liquefied, then discontinue the heating, and stir the mixture until it begins to congeal (see page 8).

Packaging and storage—Preserve Yellow Ointment in well-closed containers.

CATEGORY—Ointment base.

Oleandomycin Phosphate*



Oleandomycin Phosphate (1:1)

$C_{35}H_{61}NO_{12}.H_3PO_4$ Mol. wt. 785.87

Oleandomycin Phosphate has a potency of not less than 775 mcg. of oleandomycin base activity per mg. It conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Oleandomycin Phosphate occurs as a white, practically odorless, crystalline powder.

Solubility—Oleandomycin Phosphate is freely soluble in water and in alcohol. It is slightly soluble in ether.

Packaging and storage—Preserve Oleandomycin Phosphate in tight containers.

CATEGORY—Antibacterial.

USUAL DOSE RANGE—Intravenous, **1** to **3 g.** daily in divided doses. Intramuscular, **200 mg.** every 6 to 8 hours.

Sterile Oleandomycin Phosphate

Sterile Oleandomycin Phosphate is oleandomycin phosphate suitable for parenteral use. Sterile Oleandomycin Phosphate conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

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* Patented. See notice, page ii.

Other requirements—Sterile Oleandomycin Phosphate conforms to the statement for *Description* and *Solubility* under Oleandomycin Phosphate, page 496.

Packaging and storage—Preserve Sterile Oleandomycin Phosphate in *Containers for Sterile Solids* as described under *Injections*, page 810.

Labeling—Sterile Oleandomycin Phosphate complies with the requirements for *Labeling* under *Injections*, page 810.

Size available—Sterile Oleandomycin Phosphate is usually available in the following amount: 200 mg.

Category and Dose—See Oleandomycin Phosphate.

Oleovitamin A and D

Oleovitamin A and D is a solution of vitamin A and vitamin D in fish liver oil or in an edible vegetable oil. The vitamin D is from natural sources or is present as ergocalciferol or cholecalciferol or the products obtained by the activation of either ergosterol or 7-dehydrocholesterol. Oleovitamin A and D contains not less than 90.0 percent of the labeled amounts of vitamins A and D.

Description—Oleovitamin A and D occurs as a yellow to red oily liquid. It is a clear liquid at temperatures above 65°, and it may crystallize on cooling. Oleovitamin A and D may be nearly odorless or may have a fishlike odor. It does not have a rancid odor or taste. It is unstable in air, and in light.

Solubility—Oleovitamin A and D is insoluble in water and in glycerin. It is soluble in dehydrated alcohol and in vegetable oils, and is very soluble in ether and in chloroform.

Identification for vitamin A—Dilute sufficient Oleovitamin A and D with chloroform so that approximately 6 mcg. of vitamin A is contained in each ml. of the solution. To 1 ml. of this solution add 10 ml. of antimony trichloride T.S.: a blue color appears at once.

Assay for vitamin A—Proceed as directed under *Vitamin A Assay*, page 891.

Assay for vitamin D—Accurately measure a portion of Oleovitamin A and D expected to contain about the equivalent of 125 to 250 mcg. of vitamin D, but not more than 7.5 mg. of vitamin A, and proceed as directed under *Vitamin D Assay, Chemical Method*, page 895. If the sample contains less than the equivalent of 2.5 mcg. of vitamin D per g., or if the ratio of vitamin A to vitamin D exceeds 300 to 1, proceed as directed under *Vitamin D Assay, Biological Method*, page 895.

Packaging and storage—Preserve Oleovitamin A and D in tight containers, protected from light and air, preferably under an atmosphere of an inert gas. Store in a dry place.

Labeling—Label Oleovitamin A and D to indicate the content of vitamin A in mg. per g. The vitamin A content may also be expressed in USP units of vitamin A per g. Label Oleovitamin A and D to show whether it contains activated ergosterol, cholecalciferol, or vitamin D from a natural source. State the vitamin D content in mcg. per g. Its vitamin D content may also be expressed in USP units of vitamin D per g.

Category—Vitamins A and D supplement.

Usual dose—To be determined by the physician according to the needs of the patient.

Oleovitamin A and D Capsules

Oleovitamin A and D Capsules contain not less than 90.0 percent of the labeled amounts of vitamins A and D. The oil in Oleovitamin A and D Capsules conforms to the definition for Oleovitamin A and D, page 497.

Description—The oil contained in Oleovitamin A and D Capsules conforms to the *Description* under *Oleovitamin A and D*, page 497.

Assay for vitamin A—Transfer to a saponification flask not less than 5 Oleovitamin A and D Capsules, add 10 to 20 ml. of water, and heat for about 10 minutes. Crush any remaining solids with the blunt end of a glass rod and proceed as directed in the paragraph titled *Saponification* under *Vitamin A Assay*, page 891, beginning with "Reflux in an *all-glass* apparatus . . . ."

Assay for vitamin D—Transfer to a saponification flask not less than 5 Oleovitamin A and D Capsules, add 10 to 20 ml. of water, and heat for about 10 minutes. Crush any remaining solids with the blunt end of a glass rod and proceed as directed under *Vitamin D Assay, Chemical Method,* page 895.

The *Sample Preparation* used in the chromatographic procedures must contain not more than the equivalent of 7.5 mg. of vitamin A or less than 125 mcg. of vitamin D. If the ratio of vitamin A to vitamin D in the sample exceeds 300 to 1, proceed as directed under *Vitamin D Assay, Biological Method,* page 895.

Packaging and storage—Preserve Oleovitamin A and D Capsules in tight, light-resistant containers. Store in a dry place.

Labeling—Label Oleovitamin A and D Capsules to indicate the content in mg. of vitamin A in each capsule. The vitamin A content in each capsule may also be expressed in USP units of vitamin A. Label Oleovitamin A and D Capsules to show whether they contain activated ergosterol, cholecalciferol, or vitamin D from a natural source. State the vitamin D content in mcg. in each capsule. The vitamin D content may also be expressed in USP units of vitamin D in each capsule.

CATEGORY and DOSE—See Oleovitamin A and D.

Ophthalmic Chlortetracycline Hydrochloride, page 168
Ophthalmic Oxytetracycline Hydrochloride, page 513

Orange Flower Oil

Orange Flower Oil is the volatile oil distilled from the fresh flowers of *Citrus aurantium* Linné (Fam. *Rutaceæ*).

Description—Orange Flower Oil is a pale yellow, slightly fluorescent liquid, which becomes reddish brown on exposure to light and air. It has a distinctive, fragrant odor, similar to that of orange blossoms, and an aromatic, at first sweet, then somewhat bitter taste. Orange Flower Oil may become turbid or solid at low temperatures. It is neutral to litmus.

Solubility—Orange Flower Oil is miscible with an equal volume of alcohol and with about 2 volumes of 80 percent alcohol, the solution becoming cloudy on the further addition of alcohol of the same percentage.

Identification—An alcohol solution of Orange Flower Oil has a violet fluorescence.

Specific gravity, page 866—The specific gravity of Orange Flower Oil is not less than 0.863 and not more than 0.880.

Angular rotation, page 822—The angular rotation of Orange Flower Oil is between +1.5° and +9.1° when determined in a 100-mm. tube.

Packaging and storage—Preserve Orange Flower Oil in tight, light-resistant containers.

CATEGORY—Flavor; perfume.

Orange Flower Water

Orange Flower Water is a saturated solution of the odoriferous principles of the flowers of *Citrus aurantium* Linné (Fam. *Rutaceæ*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

Description—Orange Flower Water is nearly colorless, clear or only faintly opalescent, possessing the pleasant odor and taste of orange blossoms. It must be free from empyreuma, mustiness, and fungoid growths.

Nonvolatile residue—Evaporate 100 ml. of Orange Flower Water on a steam bath, and dry the residue at 105° for 1 hour: the weight of the residue does not exceed 15 mg. (0.015 percent).

Reaction—Orange Flower Water is neutral or only slightly acid to litmus.

Heavy metals, page 806—To 5 ml. of Orange Flower Water add 2 ml. of diluted acetic acid and water to make 25 ml.: the heavy metals limit for Orange Flower Water is 2 parts per million.

Packaging and storage—Preserve Orange Flower Water in tight containers.

CATEGORY—Vehicle; flavor; perfume.

Bitter Orange Peel

Bitter Orange Peel is the dried rind of the unripe but fully grown fruit of *Citrus aurantium* Linné (Fam. *Rutaceæ*).

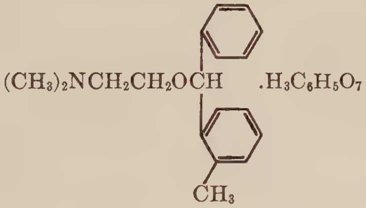
Unground Bitter Orange Peel occurs in irregular bands (ribbons) or quarters from 2 to 6 mm. in thickness; its outer surface is weak brown to moderate olive and shows numerous pits and fine reticulate ridges; its inner surface is weak yellow to weak greenish yellow with many slight conical projections and fine anastomosing lines formed by the vascular bundles; its fracture is hard and short. It has a fragrant and aromatic odor and an aromatic and bitter taste.

Histology—Sections of Bitter Orange Peel show an epidermis of small, angular cells; an outer parenchyma of thick-walled cells containing chloroplasts or chromoplasts and occasionally calcium oxalate prisms, and bearing large schizolysigenous oil reservoirs, arranged mostly in two irregular rows, and an inner spongy parenchyma of branched cells surrounding large intercellular spaces, and bearing delicate, anastomosing vascular bundles.

Powdered Bitter Orange Peel is weak yellow to weak greenish yellow. Its elements of identification are: numerous fragments of parenchyma, the cell walls from 4 to 12 μ thick; fragments of oil reservoirs with oil globules; very small vessels with close spiral markings or simple pits, and calcium oxalate prisms from 15 to 45 μ in length.

CATEGORY—Flavor.

Orphenadrine Citrate*



N,N-Dimethyl-2-[(*o*-methyl-α-phenylbenzyl)oxy]ethylamine Citrate (1:1)

$C_{18}H_{23}NO.C_6H_8O_7$ Mol. wt. 461.52

Orphenadrine Citrate contains not less than 98.0 percent and not more than 101.5 percent of $C_{18}H_{23}NO.C_6H_8O_7$, calculated on the dried basis.

Description—Orphenadrine Citrate occurs as a white, crystalline powder having a bitter taste. It is practically odorless.

Solubility—Orphenadrine Citrate is sparingly soluble in water, slightly soluble in alcohol, and insoluble in chloroform, in benzene, and in ether.

Melting range, page 814—Orphenadrine Citrate melts between 134° and 138°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Orphenadrine Citrate, previously dried at 105° for 3 hours, exhibits maxima and minima at the same wavelengths as that of NF Orphenadrine Citrate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2000 solution of Orphenadrine Citrate in alcohol exhibits maxima and minima at the same wavelengths as that of NF Orphenadrine Citrate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 264 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Orphenadrine Citrate at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Orphenadrine Citrate yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 1 g. of Orphenadrine Citrate, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 46.15 mg. of $C_{18}H_{23}NO.C_6H_8O_7$.

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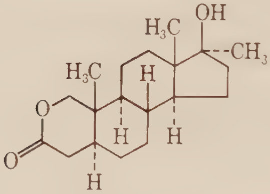
* Patented. See notice, page ii.

Packaging and storage—Preserve Orphenadrine Citrate in tight, light-resistant containers.

Category—Skeletal muscle relaxant.

Usual dose—Oral, **100 mg.** two times a day. Parenteral, **60 mg.** every 12 hours.

Oxandrolone*



17β-Hydroxy-17-methyl-2-oxa-5α-androstan-3-one

$C_{19}H_{30}O_3$ Mol. wt. 306.45

Oxandrolone contains not less than 97.0 percent and not more than 100.5 percent of $C_{19}H_{30}O_3$, calculated on the dried basis.

Description—Oxandrolone occurs as a white, odorless, crystalline powder. It is stable in air but darkens when exposed to light.

Solubility—Oxandrolone is practically insoluble in water. It is sparingly soluble in alcohol and in acetone, and is freely soluble in chloroform.

Identification—Prepare a solution of Oxandrolone in chloroform containing 500 mcg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 μl. of this solution and 10 μl. of a chloroform solution of NF Oxandrolone Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of chloroform and methanol (19:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Melting range, *Class Ia*, page 815—Oxandrolone melts between 225° and 233°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Oxandrolone, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Oxandrolone Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Oxandrolone, calculated on the dried basis, determined in a solution in chloroform containing 100 mg. of Oxandrolone in each 10 ml., is between −18° and −24°.

Loss on drying, page 814—Dry Oxandrolone at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Oxandrolone yields not more than 0.2 percent of residue on ignition.

Assay—Transfer about 500 mg. of Oxandrolone, accurately weighed, to a 250-ml. conical flask, and add 25.0 ml. of 0.1 *N* alcoholic potassium hydroxide. Insert into the neck of the flask, by means of a perforated stopper, an air condenser consisting of a glass tube 70 to 80 cm. in length and 5 to 8 mm. in diameter, and heat the flask on a steam bath for 30 minutes, frequently rotating the contents. Cool, add 1 ml. of phenolphthalein T.S., and titrate the excess alkali with 0.1 *N* hydrochloric acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* potassium hydroxide is equivalent to 30.64 mg. of $C_{19}H_{30}O_3$.

Packaging and storage—Preserve Oxandrolone in well-closed, light-resistant containers.

Category—Androgen.

Usual dose range—Initial, **5** to **10 mg.** daily; maintenance, **2.5** to **5 mg.** daily.

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* Patented. See notice, page ii.

Oxandrolone Tablets

Oxandrolone Tablets contain not less than 92.0 percent and not more than 108.0 percent of the labeled amount of $C_{19}H_{30}O_3$.

Identification—The infrared absorption spectrum of the *Assay preparation*, prepared from Oxandrolone Tablets as directed in the *Assay*, exhibits maxima at the same wavelengths as that of the *Standard preparation*, prepared as directed in the *Assay*.

Disintegration, page 878—The disintegration time limit for Oxandrolone Tablets is 15 minutes.

Content uniformity, *Method I*, page 799—Oxandrolone Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube, measuring 10 mm. in diameter, with the aid of a tamping rod having a flat disk at the end with a diameter about 1 mm. less than that of the chromatographic tube. To 0.5 g. of purified siliceous earth in a 50-ml. beaker add 0.3 ml. of 0.01 *N* hydrochloric acid, and incorporate by kneading and chopping thoroughly with a flexible spatula blade until the mixture is fluffy. Transfer to the tube, and tamp gently to compress the mixture to a uniform mass.

Standard preparation—Transfer about 12.5 mg. of NF Oxandrolone Reference Standard, accurately weighed, to a 10-ml. volumetric flask, add chloroform to volume, and mix.

Assay preparation—Weigh and finely powder not less than 20 Oxandrolone Tablets. Transfer to a 50-ml. beaker an accurately weighed portion of the powder, equivalent to about 2.5 mg. of oxandrolone, and add 0.1 ml. of dimethyl sulfoxide. Mix with a spatula until the powder is thoroughly wetted, and add 500 mg. of purified siliceous earth and 0.5 ml. of 0.01 *N* hydrochloric acid. Mix as directed under *Chromatographic column*, and transfer to the prepared column in two portions, tamping gently after each addition. Dry wash the beaker with an additional portion of adsorbent, transfer it to the column, and gently compress with the tamping rod. Place a pledget of fine glass wool on top of the column. Elute the oxandrolone with 150 ml. of water-washed chloroform, collecting the eluate in a suitable vessel. Evaporate to dryness on a steam bath in a current of air. Dissolve the residue in a few ml. of chloroform, transfer to a 10-ml. conical flask, and again evaporate to dryness. Add 2.0 ml. of chloroform, and mix.

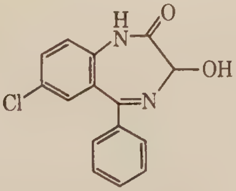
Procedure—Concomitantly determine the absorbances of the solutions, in 1-mm. cells, at the maximum at about 5.78 μ, with a suitable spectrophotometer, using a procedural blank in the reference cell. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{19}H_{30}O_3$ in the portion of the Tablets taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Oxandrolone Tablets in tight, light-resistant containers.

Tablets available—Oxandrolone Tablets usually available contain the following amount of oxandrolone: 2.5 mg.

Category and Dose—See Oxandrolone.

Oxazepam*



7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one

$C_{15}H_{11}ClN_2O_2$ Mol. wt. 286.72

Oxazepam contains not less than 98.0 percent and not more than 102.0 percent of $C_{15}H_{11}ClN_2O_2$, calculated on the dried basis.

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* Patented. See notice, page ii.

Description—Oxazepam occurs as a creamy white to pale yellow powder. It is practically odorless.

Solubility—Oxazepam is slightly soluble in alcohol and in chloroform, and is very slightly soluble in ether. It is practically insoluble in water.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Oxazepam, previously dried at 105° in vacuum maintaining the pressure below 5 mm. of mercury for 3 hours, exhibits maxima only at the same wavelengths as that of NF Oxazepam Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 250,000 solution of Oxazepam in alcohol exhibits maxima and minima at the same wavelengths as that of NF Oxazepam Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 229 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a 1 in 50 suspension of Oxazepam in water is between 4.8 and 7.0.

Loss on drying, page 814—Dry Oxazepam at 105° in vacuum, maintaining the pressure below 5 mm. of mercury, for 3 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Oxazepam yields not more than 0.3 percent of residue on ignition.

Assay—Transfer about 400 mg. of Oxazepam, accurately weighed, to a tall-form beaker, dissolve in 100 ml. of dimethylformamide, and titrate with 0.1 *N* tetrabutylammonium hydroxide determining the end-point potentiometrically, using glass and calomel electrodes. Each ml. of 0.1 *N* tetrabutylammonium hydroxide is equivalent to 28.67 mg. of $C_{15}H_{11}ClN_2O_2$.

Packaging and storage—Preserve Oxazepam in well-closed containers.

Category—Tranquilizer (minor).

Usual dose—**10 mg.** to **15 mg.** three or four times a day.

Usual dose range—**10 mg.** to **30 mg.**

Oxazepam Capsules

Oxazepam Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{11}ClN_2O_2$.

Identification—The solution prepared for measurement of absorbance in the *Assay* exhibits a maximum at 229 ± 2 mμ.

Content uniformity, *Method I,* page 798—Oxazepam Capsules meet the requirement of the content uniformity test for capsules.

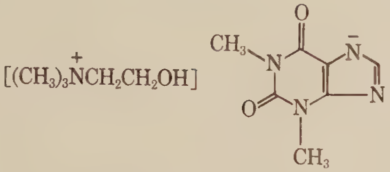
Assay—Remove, as completely as possible, the contents of not less than 20 Oxazepam Capsules, and weigh. Transfer an accurately weighed quantity of mixed powder, equivalent to about 50 mg. of oxazepam, to a medium-porosity sintered-glass funnel that is fitted into a small suction flask. Add 25 ml. of alcohol, mix well with the aid of a stirring rod, and after about 5 minutes apply gentle suction to remove the extract. Repeat the extraction with four additional 25-ml. portions of alcohol, transfer the extracts quantitatively to a 250-ml. volumetric flask, dilute to volume with alcohol, and mix. Transfer 2.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Oxazepam Reference Standard, in the same medium, at a concentration of about 4 mcg. per ml., in 1-cm. cells, at the maximum at about 229 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{15}H_{11}ClN_2O_2$ in the portion of the Capsules taken by the formula $12.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Oxazepam Capsules in well-closed containers.

Capsules available—Oxazepam Capsules usually available contain the following amounts of oxazepam: 10, 15, and 30 mg.

Category and Dose—See Oxazepam.

Oxtriphylline*



Choline Theophyllinate

$C_{12}H_{21}N_5O_3$ Mol. wt. 283.33

Oxtriphylline contains not less than 41.9 percent and not more than 43.6 percent of $C_5H_{15}NO_2$ (choline), and not less than 61.7 percent and not more than 65.5 percent of $C_7H_8N_4O_2$ (theophylline), calculated on the dried basis.

Description—Oxtriphylline occurs as a white, crystalline powder having an amine-like odor. A solution of Oxtriphylline (1 in 100) has a pH of about 10.3.

Solubility—Oxtriphylline is freely soluble in water and in alcohol. It is very slightly soluble in chloroform.

Identification—Dissolve about 1 g. of Oxtriphylline in 20 ml. of water, and divide the solution into two 10-ml. portions.

A: To 10 ml. of the test solution add 5 ml. of mercuric potassium iodide T.S.: a pale yellow precipitate forms (*presence of choline*).

B: To 10 ml. of the test solution add 5 drops of ammonia T.S. and 5 ml. of silver nitrate T.S.: a gelatinous precipitate forms which coagulates on heating (*presence of theophylline*).

Melting range, page 814—Oxtriphylline melts between 185° and 189°.

Loss on drying, page 814—Dry Oxtriphylline at 80° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Oxtriphylline yields not more than 0.3 percent of residue on ignition.

Chloride, page 784—A 500-mg. portion of Oxtriphylline shows no more chloride than corresponds to 0.15 ml. of 0.02 *N* hydrochloric acid (0.01 percent).

Assay for choline—Dissolve about 900 mg. of Oxtriphylline, accurately weighed, in 50 ml. of water, and add 4 drops of a solution prepared by dissolving 30 mg. of methyl red in 100 ml. of methanol, adding 15 ml. of a 1 in 1000 solution of methylene blue, and mixing. Mix, and titrate with 0.1 *N* sulfuric acid to a purple end-point. Each ml. of 0.1 *N* sulfuric acid is equivalent to 12.12 mg. of $C_5H_{15}NO_2$. Retain the final solution for the *Assay for theophylline.*

Assay for theophylline—To the solution retained in the *Assay for choline,* add 35 ml. of silver nitrate T.S., swirl gently to promote complete precipitation, and titrate with 0.1 *N* sodium hydroxide to a green end-point. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 18.02 mg. of $C_7H_8N_4O_2$.

Packaging and storage—Preserve Oxtriphylline in tight containers, protected from heat.

CATEGORY—Bronchodilator.
USUAL DOSE—**200 mg.** four times a day.
USUAL DOSE RANGE—**200** to **400 mg.**

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* Patented. See notice, page ii.

Oxtriphylline Tablets

Oxtriphylline Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{12}H_{21}N_5O_3$. Oxtriphylline Tablets may be uncoated or partially enteric-coated.

Identification—Extract a portion of finely powdered Oxtriphylline Tablets, equivalent to about 300 mg. of oxtriphylline, with three 15-ml. portions of alcohol. (NOTE—If the tablets are coated, remove the coating by washing with water, and then dry in the air before powdering.) Filter the combined extracts through Whatman No. 42 or equivalent filter paper, evaporate the filtrate to dryness, and dissolve the residue in 10 ml. of water. Add 5 ml. of mercuric-potassium iodide T.S. to the solution so obtained: a yellow precipitate forms.

Disintegration, page 878—The disintegration time limit for uncoated Oxtriphylline Tablets is 20 minutes. Test Oxtriphylline Tablets labeled as being partially enteric-coated as directed for *Enteric-Coated Tablets,* page 878: the tablets do not disintegrate after 30 minutes of agitation in simulated gastric fluid T.S.; continue agitation in simulated gastric fluid T.S. for an additional 30 minutes: the tablets may disintegrate during this period; if all of the tablets have not disintegrated, place the basket in simulated intestinal fluid T.S., and operate the apparatus: all of the tablets disintegrate within 90 minutes (2.5 hours total disintegration time).

Weight variation, page 901—Oxtriphylline Tablets meet the requirements of the weight variation test for tablets.

Assay—[NOTE—In this assay use chloroform recently saturated with water.]

Standard preparation—Transfer about 75 mg. of NF Oxtriphylline Reference Standard, accurately weighed, to a 200-ml. volumetric flask, add a 1 in 100 solution of glacial acetic acid in chloroform to volume, and mix. Transfer 3.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with a 1 in 100 solution of glacial acetic acid in chloroform, and mix.

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (22 × 250-mm. tube to which is fused a 5-cm. length of 7-mm. tubing) with the aid of a tamping rod about 45 cm. in length and having a disk with a diameter about 1 mm. less than that of the tube. To 500 mg. of purified siliceous earth in a 100-ml. beaker add 0.3 ml. of 2 *N* tribasic sodium phosphate, and incorporate by kneading thoroughly to a uniform mixture. Transfer to the tube, and pack lightly with the tamping rod.

Assay preparation—Weigh and finely powder not less than 20 Oxtriphylline Tablets. Transfer to a 100-ml. beaker an accurately weighed portion of the powder, equivalent to about 75 mg. of oxtriphylline, add 2.0 ml. of 2 *M* tribasic sodium phosphate, and mix well. Add 3 g. of purified siliceous earth, mix thoroughly, and transfer quantitatively to the column in three portions, packing each portion uniformly. Cover the column with a pledget of fine glass wool, and pack lightly. Wash the column with three 25-ml. portions of chloroform, allowing each portion to enter the column before adding the next, and discard the washings. Elute the theophylline with 5 ml. of a 1 in 10 solution of glacial acetic acid in chloroform, followed by 150 ml. of a 1 in 100 solution of glacial acetic acid in chloroform, collecting the eluates in a 200-ml. volumetric flask. Dilute to volume with a 1 in 100 solution of glacial acetic acid in chloroform, and mix. Transfer 3.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with a 1 in 100 solution of glacial acetic acid in chloroform, and mix.

Procedure—Concomitantly determine the absorbance of the *Standard preparation* and of the *Assay preparation* in 1-cm. cells, at the maximum at about 277 mμ, with a suitable spectrophotometer, using a 1 in 100 solution of glacial acetic acid in chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{12}H_{21}N_5O_3$ in the portion of Tablets taken by the formula $6.67C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

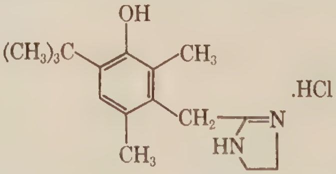
Packaging and storage—Preserve Oxtriphylline Tablets in tight containers, protected from heat and moisture.

Labeling—Label Oxtriphylline Tablets to indicate whether they are uncoated or partially enteric-coated.

Tablets available—Oxtriphylline Tablets usually available contain the following amounts of oxtriphylline: 100 and 200 mg.

CATEGORY and DOSE—See Oxtriphylline.

Oxymetazoline Hydrochloride*



6-*tert*-Butyl-3-(2-imidazolin-2-ylmethyl)-2,4-dimethylphenol Monohydrochloride

$C_{16}H_{24}N_2O \cdot HCl$ Mol. wt. 296.84

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* Patented. See notice, page ii.

Oxymetazoline Hydrochloride, dried at 105° for 3 hours, contains not less than 98.5 percent and not more than 101.5 percent of $C_{16}H_{24}N_2O.HCl$.

Description—Oxymetazoline Hydrochloride occurs as a white to nearly white, fine crystalline powder. It melts at about 300° with decomposition (*Class Ia*, page 815).

Solubility—Oxymetazoline Hydrochloride is soluble in water and in alcohol. It is practically insoluble in benzene, in chloroform, and in ether.

Identification—

A: Dissolve about 2 mg. of Oxymetazoline Hydrochloride in 1 ml. of water, add a few drops of sodium nitroferricyanide T.S. and 2 drops of sodium hydroxide solution (15 in 100), mix, and allow to stand for 10 minutes. Add 0.1 *N* hydrochloric acid dropwise until the pH is between 8 and 9, and allow to stand for 10 minutes: a violet color develops.

B: To a solution of about 50 mg. of Oxymetazoline Hydrochloride in 3 ml. of water, add ammonia T.S., filter, and acidify the filtrate with nitric acid: the filtrate responds to the tests for *Chloride*, page 808.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Oxymetazoline Hydrochloride, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Oxymetazoline Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 10,000 solution of Oxymetazoline Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Oxymetazoline Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 279 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of a solution of Oxymetazoline Hydrochloride (1 in 20) is between 4.0 and 6.5.

Loss on drying, page 814—Dry Oxymetazoline Hydrochloride at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Oxymetazoline Hydrochloride yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Oxymetazoline Hydrochloride is 10 parts per million.

Assay—Dissolve about 600 mg. of Oxymetazoline Hydrochloride, previously dried at 105° for 3 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S. and 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 29.68 mg. of $C_{16}H_{24}N_2O.HCl$.

Packaging and storage—Preserve Oxymetazoline Hydrochloride in tight containers.

CATEGORY—Adrenergic (vasoconstrictor).

APPLICATION—Nasally, 2 to 4 drops of a 0.05 percent solution instilled into each nostril twice a day.

Oxymetazoline Hydrochloride Solution

Oxymetazoline Hydrochloride Solution is a solution of oxymetazoline hydrochloride in water adjusted to a suitable pH and tonicity. It contains not less than 95.0 percent and not more than 115.0 percent of the labeled amount of $C_{16}H_{24}N_2O.HCl$.

Identification—Oxymetazoline Hydrochloride Solution responds to *Identification test A* under *Oxymetazoline Hydrochloride*, page 504.

pH, page 824—The pH of Oxymetazoline Hydrochloride Solution is between 5.5 and 6.5.

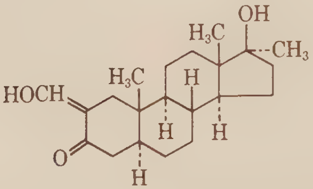
Assay—Transfer an accurately measured volume of Oxymetazoline Hydrochloride Solution, equivalent to about 5 mg. of oxymetazoline hydrochloride, to a separator, add 25 ml. of a saturated solution of sodium borate, and extract with four 25-ml. portions of chloroform, combining the extracts in a second separator. Extract the combined chloroform extracts with two 20-ml. portions of 0.5 *N* hydrochloric acid, combine the acid extracts in a 100-ml. volumetric flask, dilute to volume with the 0.5 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Oxymetazoline Hydrochloride Reference Standard, in the same medium at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 279 mμ, with a suitable spectrophotometer, using 0.5 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{16}H_{24}N_2O.HCl$ in each ml. of the Solution taken, by the formula 0.1 × (C/V) × (A_U/A_S), in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Solution taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Oxymetazoline Hydrochloride Solution in tight containers.

Solution available—Oxymetazoline Hydrochloride Solution usually available contains 0.05 percent of oxymetazoline hydrochloride.

CATEGORY and APPLICATION—See Oxymetazoline Hydrochloride.

Oxymetholone*



17β-Hydroxy-2-(hydroxymethylene)-17-methyl-5α-androstan-3-one

$C_{21}H_{32}O_3$ Mol. wt. 332.49

Oxymetholone contains not less than 97.0 percent and not more than 103.0 percent of $C_{21}H_{32}O_3$, calculated on the dried basis.

Description—Oxymetholone occurs as a white to creamy white crystalline powder. It is odorless and is stable in air.

Solubility—Oxymetholone is practically insoluble in water. It is sparingly soluble in alcohol, freely soluble in chloroform, soluble in dioxane, and slightly soluble in ether.

Completeness of solution—Dissolve 100 mg. of Oxymetholone in 5 ml. of dioxane: the solution is clear and free from undissolved solid.

Melting range, *Class Ia*, page 815—Oxymetholone melts between 174° and 182°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Oxymetholone, previously dried in vacuum over phosphorus pentoxide for 4 hours, exhibits maxima only at the same wavelengths as that of NF Oxymetholone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Oxymetholone in 0.01 *N* methanolic sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Oxymetholone Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Oxymetholone, calculated on the dried basis, determined in a solution in dioxane containing 200 mg. of Oxymetholone in each 10 ml., is between +34° and +38°.

Loss on drying, page 814—Dry Oxymetholone in vacuum over phosphorus pentoxide for 4 hours: it loses not more than 1 percent of its weight.

Foreign steroids and other impurities—*Standard preparation*—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Oxymetholone Reference Standard, previously dried in vacuum over phosphorus pentoxide for 4 hours.

Test preparation—Weigh accurately about 80 mg. of Oxymetholone previously dried in vacuum over phosphorus pentoxide for 4 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and alcohol (98:2), and determining the absorbance at the maximum at about 315 mμ. (Note: Use 0.01 *N* alcoholic sodium hydroxide, rather than alcohol, to elute the silica gel bands.) Calculate the percentage of chromatographic impurities by the formula 100 − [100 × 10 × (C/W) × (A_U/A_S)], in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Oxymetholone taken: not more than 3 percent is found.

Assay—Transfer about 100 mg. of Oxymetholone, accurately weighed, to a 200-ml. volumetric flask, add 0.01 *N* methanolic sodium hydroxide to volume, and mix. Transfer 5.0 ml. of the solution to a 250-ml. volumetric flask, dilute to volume with 0.01 *N* methanolic sodium hydroxide, and mix. Without delay concomitantly determine the absorbance of this solution and of a freshly prepared solution of NF Oxymetholone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 315 mμ, with a suitable spectrophotometer, using 0.01 *N* methanolic sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_{21}H_{32}O_3$ in the Oxymetholone taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Oxymetholone in well-closed containers.

CATEGORY—Androgen.
USUAL DOSE—**5** to **10 mg.** daily.
USUAL DOSE RANGE—**5** to **30 mg.**

Oxymetholone Tablets

Oxymetholone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{32}O_3$.

Identification—Mix an amount of powdered Oxymetholone Tablets, equivalent to about 50 mg. of oxymetholone, with 15 ml. of solvent hexane, and stir occasionally for 15 minutes. Centrifuge the mixture, then decant and discard the solvent hexane. Extract the residue with two additional 10-ml. portions of solvent hexane, centrifuging and decanting as before, and discard the solvent hexane. Add 25 ml. of chloroform to the residue, mix by shaking for 1 to 2 minutes, and filter. Evaporate the filtrate to about 3 ml., add a few ml. of solvent hexane to induce crystallization, and evaporate to dryness: the infrared absorption spectrum of a potassium bromide dispersion prepared from the residue so obtained exhibits maxima only at the same wavelengths as that of NF Oxymetholone Reference Standard, crystallized from the same solvent mixture and similarly measured.

Disintegration, page 878—The disintegration time limit for Oxymetholone Tablets is 30 minutes.

Content Uniformity, *Method II,* page 799—Oxymetholone Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered Tablet to a 100-ml. volumetric flask with the aid of about 75 ml. of methanol. Heat the methanol to boiling, and allow to remain at a temperature just below the boiling point for 15 minutes with occasional swirling. Cool to room temperature, dilute to volume with methanol, and mix. Centrifuge a portion of the mixture at about 2000 r.p.m. until the solution becomes clear. Dilute a portion of the supernatant liquid quantitatively and stepwise, if necessary, with methanol and sufficient 0.1 *N* methanolic sodium hydroxide to provide a solution in 0.01 *N* methanolic sodium hydroxide containing approximately 10 mcg. of oxymetholone per ml. Concomitantly determine the absorbance of this solution and of a freshly prepared solution of NF Oxymetholone Reference Standard in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 315 mμ, with a suitable spectrophotometer, using 0.01 *N* methanolic sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_{21}H_{32}O_3$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of oxymetholone in the tablet; D is the exact concentration, in mcg. per ml., of oxymetholone in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

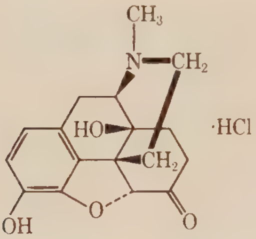
Assay—Weigh and finely powder not less than 20 Oxymetholone Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of oxymetholone, to a separator, add 10 ml. of water, and extract with three 25-ml. portions of chloroform, filtering each extract through chloroform-washed cotton. Evaporate the combined chloroform extracts to dryness on a steam bath, reducing the application of heat as dryness is approached. Dissolve the residue in methanol, transfer to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 5.0 ml. of the solution to a 100-ml. volumetric flask, add 10 ml. of 0.1 *N* methanolic sodium hydroxide, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a freshly prepared solution of NF Oxymetholone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 315 mμ, with a suitable spectrophotometer, using 0.01 *N* methanolic sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_{21}H_{32}O_3$ in the portion of the Tablets taken by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Oxymetholone Tablets in well-closed containers.

Tablets available—Oxymetholone Tablets usually available contain the following amounts of oxymetholone: 2.5, 5, and 10 mg.

Category and Dose—See Oxymetholone.

Oxymorphone Hydrochloride*



4,5*a*-Epoxy-3,14-dihydroxy-17-methylmorphinan-6-one Hydrochloride

$C_{17}H_{19}NO_4.HCl$ Mol. wt. 337.81

Oxymorphone Hydrochloride contains not less than 97.0 percent and not more than 102.0 percent of $C_{17}H_{19}NO_4.HCl$, calculated on the dried basis.

Description—Oxymorphone Hydrochloride occurs as a white or slightly off-white, odorless powder. It darkens on exposure to light. Its aqueous solutions are slightly acidic.

Solubility—Oxymorphone Hydrochloride is freely soluble in water. It is sparingly soluble in alcohol and in ether.

Identification—

A: Dissolve about 250 mg. of Oxymorphone Hydrochloride in 25 ml. of water, and make the solution alkaline with a saturated solution of sodium bicarbonate. Extract the liberated base with two 15-ml. portions of chloroform, and reserve the aqueous phase for *Identification test B*. Combine the chloroform extracts in a second separator, wash with 5 ml. of water, and filter. Evaporate nearly to dryness on a steam bath, then add a few ml. of ether, and continue the evaporation with stirring until the solvent is removed: the residue of oxymorphone so obtained, dried at 105° for 1 hour, melts to a black liquid between 246° and 251° (*Class Ia*, page 815).

B: The aqueous phase from *Identification test A*, when acidified with diluted nitric acid, responds to the tests for *Chloride*, page 808.

C: Dissolve 10 mg. of Oxymorphone Hydrochloride in 1 ml. of water, and add a few drops of ferric chloride T.S.: a blue color is produced immediately.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 50 solution in chloroform of oxymorphone base, prepared as directed in *Identification test A*, determined in a 0.5-cm. cell, exhibits maxima, among others, at the following approximate wavelengths, in μ: 3.43 (*s*), 5.85 (*vs*), 6.15 (*w*), 6.25 (*m*), 6.7 (*vs*), 6.9 (*vs*), 7.6 (*s*), 7.8 (*m*), 7.9 (*m*), 8.1 (*s*), 8.5 (*s*), 8.65 (*m*), 8.76 (*vs*), 8.85 (*w*), 9.0 (*s*), 9.3 (*w*), 9.5 (*s*), 9.6 (*s*), 9.7 (*s*), 10.1 (*vs*), 10.3 (*m*), 10.5 (*s*), 10.6 (*vs*), 10.9 (*s*), 11.3 (*s*), 11.8 (*s*), and 12.3 (*s*).

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 6500 solution of Oxymorphone Hydrochloride in 0.1 N hydrochloric acid exhibits a maximum at 281 ± 2 mμ, and a minimum at 264 ± 2 mμ. The ratio A_{281}/A_{264} is 1.85 ± 0.2.

Specific rotation, page 822—The specific rotation of Oxymorphone Hydrochloride, determined in a solution in water containing 1 g. of Oxymorphone Hydrochloride in each 10 ml., calculated on the dried basis, is between −145° and −155°.

Acidity—Dissolve 300 mg. of Oxymorphone Hydrochloride in 10 ml. of water, add 1 drop of methyl red T.S., and titrate with 0.02 N sodium hydroxide: not more than 0.3 ml. is required to produce a yellow color.

Loss on drying, page 814—Dry Oxymorphone Hydrochloride for 18 hours at 105°: it loses not more than 8 percent of its weight.

Residue on ignition, page 858—The

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* Patented. See notice, page ii.

residue on ignition from 200 mg. of Oxymorphone Hydrochloride is negligible.

Chloride—Dissolve about 300 mg. of Oxymorphone Hydrochloride, accurately weighed, in 50 ml. of methanol in a glass-stoppered flask, add 5 ml. of glacial acetic acid and 3 drops of eosin Y T.S., and titrate with 0.1 *N* silver nitrate. Each ml. of 0.1 *N* silver nitrate is equivalent to 3.546 mg. of Cl: not less than 10.2 percent and not more than 10.8 percent is found, calculated on the dried basis.

Nonphenolic substances—Dissolve 1 g. of Oxymorphone Hydrochloride in 15 ml. of water, add 5 ml. of 2 *N* sodium hydroxide, and extract with three 10-ml. portions of chloroform. Filter the combined extracts through a small chloroform-moistened filter paper, and wash the filtrate with 5 ml. of water. Filter the chloroform layer through chloroform-moistened filter paper into a tared 50-ml. beaker, and evaporate to dryness on a steam bath with the aid of a gentle stream of filtered air. Dry the beaker and residue at 105° for 1 hour, and weigh: the residue so obtained does not exceed 15 mg.

Assay—Transfer about 700 mg. of Oxymorphone Hydrochloride, accurately weighed, to a glass-stoppered flask containing 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S. Add 3 ml. of acetic anhydride and 1 drop of methyl violet T.S., and titrate with 0.1 *N* perchloric acid in dioxane to a clear blue color. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 33.78 mg. of $C_{17}H_{19}NO_4.HCl$.

Packaging and storage—Preserve Oxymorphone Hydrochloride in tight, light-resistant containers.

CATEGORY—Analgesic (narcotic).

USUAL DOSE—Oral, **10 mg.** every 4 to 6 hours, with a maximum dose of **40 mg.** per day; subcutaneously and intramuscularly, **1.0** to **1.5 mg.** every 4 to 6 hours as needed; intravenous, **0.5 mg.** initially, repeated in 4 to 6 hours if necessary.

Oxymorphone Hydrochloride Injection

Oxymorphone Hydrochloride Injection is a sterile solution of oxymorphone hydrochloride in water for injection. It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{17}H_{19}NO_4.HCl$.

Identification—The solution prepared for measurement of absorbance as directed in the *Assay* exhibits a maximum at 282 ± 2 mμ.

pH, page 824—The pH of Oxymorphone Hydrochloride Injection is between 2.7 and 4.5.

Other requirements—Oxymorphone Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—

Standard preparation—Transfer about 45 mg. of oxymorphone base, accurately weighed, obtained as directed in *Identification test A* under *Oxymorphone Hydrochloride,* page 508, to a 50-ml. volumetric flask, dissolve in about 10 ml. of chloroform, add chloroform to volume, and mix. Transfer 15.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparation—Transfer an accurately measured volume of Oxymorphone Hydrochloride Injection, equivalent to about 15 mg. of oxymorphone hydrochloride, to a 125-ml. separator, and add sufficient water to bring the volume to 15 ml. Adjust the pH to less than 2 by the addition of hydrochloric acid, and extract with five 15-ml. portions of chloroform, collecting the extracts in a second separator. Shake the combined chloroform extracts with 10 ml. of water, discard the chloroform, and combine the water layer with the aqueous solution in the first separator. Adjust the pH of the aqueous phase to 9.5 with stronger ammonia water, and extract with four 20-ml. portions of chloroform. Filter the chloroform extracts into a 100-ml. volumetric flask through a chloroform-moistened pledget of cotton, dilute to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 282 mμ, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{17}H_{19}NO_4.HCl$ in each ml. of the Injection taken by the formula $0.1 \times 1.121 \times (C/V) \times (A_U/A_S)$, in which 1.121 is a factor converting oxymorphone base to the hydrochloride, C is the exact concentration, in mcg. per ml., of oxymorphone base in the *Standard preparation*, and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Oxymorphone Hydrochloride Injection in single-dose or in multiple-dose containers of Type I glass, protected from light.

Injections available—Oxymorphone Hydrochloride Injection usually available contains the following amounts of oxymorphone hydrochloride: 1.0 mg. in 1 ml.; 1.5 mg. in 1.5 ml.; 3 mg. in 2 ml.; 15 mg. in 10 and 15 ml.

Category and Dose—See Oxymorphone Hydrochloride.

Oxymorphone Hydrochloride Tablets

Oxymorphone Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{17}H_{19}NO_4.HCl$.

Identification—The solution prepared for measurement of absorbance in the *Assay* exhibits a maximum at 282 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Oxymorphone Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Oxymorphone Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Oxymorphone Hydrochloride Injection,* page 509.

Assay preparation—Weigh and finely powder not less than 20 Oxymorphone Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg. of oxymorphone hydrochloride, to a 100-ml. volumetric flask, add 60 ml. of water and 1 drop of hydrochloric acid T.S., and shake for 30 minutes. Dilute to volume with water, mix, and filter, discarding the first 25 ml. of filtrate. Transfer 15.0 ml. of the subsequent filtrate to a 125-ml. separator. Adjust the pH to 9.5 with stronger ammonia water, and extract with our 20-ml. portions of chloroform. Filter the chloroform extracts through chloroform-moistened cotton into a 100-ml. volumetric flask, dilute to volume with chloroform and mix.

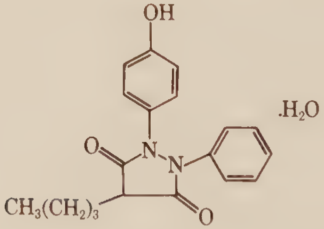
Procedure—Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 282 mμ, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{17}H_{19}NO_4.HCl$ in the portion of Tablets taken by the formula $0.667C \times 1.121 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of oxymorphone base in the *Standard preparation,* and 1.121 is a factor converting oxymorphone base to the hydrochloride.

Packaging and storage—Preserve Oxymorphone Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Oxymorphone Hydrochloride Tablets usually available contain the following amount of oxymorphone hydrochloride: 10 mg.

Category and Dose—See Oxymorphone Hydrochloride.

Oxyphenbutazone*



4-Butyl-1-(*p*-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione

$C_{19}H_{20}N_2O_3.H_2O$ Mol. wt. 342.40

Oxyphenbutazone contains not less than 98.0 percent and not more than 100.5 percent of $C_{19}H_{20}N_2O_3$, calculated on the anhydrous basis.

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* Patented. See notice, page ii.

Description—Oxyphenbutazone occurs as a white to yellowish white, odorless, crystalline powder. It melts over a wide range between about 85° and 100°.

Solubility—Oxyphenbutazone is very slightly soluble in water. It is soluble in alcohol, and is freely soluble in acetone and in ether.

Identification—Dissolve about 20 mg. of Oxyphenbutazone in 2 ml. of methanol, and add 3 ml. of Millon's reagent: a precipitate, which turns cherry red when the mixture is heated, is formed.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 50 solution of Oxyphenbutazone, previously dried over a suitable desiccant, in methylene chloride exhibits maxima only at the same wavelengths as that of NF Oxyphenbutazone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Oxyphenbutazone in 0.01 N sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Oxyphenbutazone Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance occurring at about 254 $m\mu$, do not differ by more than 2 percent.

Water, page 900—Determine the water content of Oxyphenbutazone by the titrimetric method: not less than 5 percent and not more than 6 percent is found.

Residue on ignition, page 858—Oxyphenbutazone yields not more than 0.05 percent of residue on ignition.

Chloride—Boil 1 g. of Oxyphenbutazone with 20 ml. of water for 5 minutes, cool, and filter. If the filtrate is not clear, add a few mg. of talc, boil again, cool, and filter. To 1 ml. of the filtrate add 1 ml. of dilute nitric acid (1 in 6) and 1 ml. of silver nitrate T.S.: no opalescence is produced.

Assay—Dissolve about 500 mg. of Oxyphenbutazone, accurately weighed, in 25 ml. of acetone, add 5 drops of bromothymol blue T.S., and immediately titrate with 0.1 N sodium hydroxide to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N sodium hydroxide is equivalent to 32.44 mg. of $C_{19}H_{20}N_2O_3$.

Packaging and storage—Preserve Oxyphenbutazone in tight containers.

CATEGORY—Antiarthritic; anti-inflammatory (nonsteroid).

USUAL DOSE—**400 mg.** daily in divided doses.

USUAL DOSE RANGE—**100** to **600 mg.**

Oxyphenbutazone Tablets

Oxyphenbutazone Tablets contain not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{19}H_{20}N_2O_3 \cdot H_2O$.

Identification—Mix a portion of powdered Oxyphenbutazone Tablets, equivalent to about 300 mg. of oxyphenbutazone, with 20 ml. of ether, and boil on a steam bath for 2 to 3 minutes. Filter the hot mixture, wash the residue with two 5-ml. portions of hot ether, and concentrate the filtrate on a steam bath to about 12 ml. Add 12 ml. of solvent hexane, again concentrate on a steam bath to about 12 ml., and cool. Filter the mixture, wash the crystals with two 5-ml. portions of solvent hexane, and dry the crystals in vacuum at 100° for 30 minutes: the oxyphenbutazone (anhydrous) so obtained melts within a range of 3° between 115° and 124°, page 814, and responds to the *Identification test* under *Oxyphenbutazone*, page 510.

Disintegration, page 878—The disintegration time limit for Oxyphenbutazone Tablets, using simulated gastric fluid T.S. as the test medium in place of water, is 30 minutes.

Weight variation, page 901—Oxyphenbutazone Tablets meet the requirements of the weight variation test for tablets.

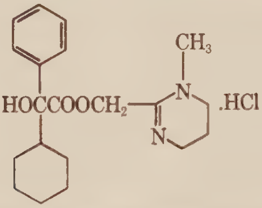
Assay—Weigh and finely powder not less than 20 Oxyphenbutazone Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg. of oxyphenbutazone, to a 250-ml. separator, add 100 ml. of ether, and shake mechanically for 15 minutes. Filter through a fine-porosity sintered-glass funnel into a 250-ml. separator, rinsing the flask and funnel with ether and collecting the rinsings in the separator. Extract the ether solution with three 30-ml. portions of 0.1 N sodium hydroxide, collecting the extracts in a 100-ml. volumetric flask. Dilute to volume with 0.01 N sodium hydroxide, mix, and filter, discarding the first 25 ml. of filtrate. Transfer 10.0 ml. of the subsequent filtrate to a second 100-ml. volumetric flask, dilute to volume with 0.01 N sodium hydroxide, and mix. Finally, transfer 10.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with 0.01 N sodium hydroxide, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Oxyphenbutazone Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 254 mμ, with a suitable spectrophotometer, using 0.01 *N* sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_{19}H_{20}N_2O_3 . H_2O$ in the portion of Tablets taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Oxyphenbutazone Tablets in tight containers.

Tablets available—Oxyphenbutazone Tablets usually available contain the following amount of oxyphenbutazone: 100 mg.

Category and Dose—See Oxyphenbutazone.

Oxyphencyclimine Hydrochloride*



(1,4,5,6-Tetrahydro-1-methyl-2-pyrimidinyl)methyl α-Phenylcyclohexaneglycolate Monohydrochloride

$C_{20}H_{28}N_2O_3 . HCl$ Mol. wt. 380.92

Oxyphencyclimine Hydrochloride, dried in vacuum at 60° for 2.5 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_{20}H_{28}N_2O_3 . HCl$.

Description—Oxyphencyclimine Hydrochloride occurs as a white, odorless, crystalline powder having a characteristic bitter taste.

Solubility—Oxyphencyclimine Hydrochloride is sparingly soluble in water. It is soluble in methanol and slightly soluble in chloroform.

Identification—Prepare a solution of Oxyphencyclimine Hydrochloride in 0.01 *N* methanolic hydrochloric acid containing 4 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.5-mm. layer of silica gel G, spot 100 μl. of this solution and 100 μl. of a solution of NF Oxyphencyclimine Hydrochloride Reference Standard in 0.01 *N* methanolic hydrochloric acid containing 4 mg. per ml. Develop the chromatogram in a solvent system of chloroform-methanol (65:27), until the solvent front has moved to within 2.5 cm. from the top of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with a mixture of 1 part of a 3 in 1000 solution of blue tetrazolium in alcohol and 2 parts of a 1 in 10 sodium hydroxide solution, then expose the sprayed plate to shortwave ultraviolet light for about 10 minutes: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Melting range, *Class Ia*, page 815—Oxyphencyclimine Hydrochloride melts between 227° and 237°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Oxyphencyclimine Hydrochloride, previously dried in vacuum at 60° for 2.5 hours, exhibits maxima only at the same wavelengths as that of NF Oxyphencyclimine Hydrochloride Reference Standard, similarly measured.

Loss on drying, page 814—Dry Oxyphencyclimine Hydrochloride in vacuum at 60° for 2.5 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Oxyphencyclimine Hydrochloride yields not more than 0.2 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Oxyphencyclimine Hydrochloride is 50 parts per million.

Assay—Dissolve about 300 mg. of Oxyphencyclimine Hydrochloride, previously dried in vacuum at 60° for 2.5 hours and accurately weighed, in 20 ml. of chloroform, add 50 ml. of glacial acetic acid, 10 ml. of mercuric acetate T.S., and 2 drops of quinaldine red T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 38.09 mg. of $C_{20}H_{28}N_2O_3 . HCl$.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Oxyphencyclimine Hydrochloride in tight containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**10 mg.** two times a day.

USUAL DOSE RANGE—**10** to **50 mg.** daily, in divided doses.

Oxyphencyclimine Hydrochloride Tablets

Oxyphencyclimine Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{28}N_2O_3 . HCl$.

Identification—Transfer an amount of finely powdered Oxyphencyclimine Hydrochloride Tablets, equivalent to about 100 mg. of oxyphencyclimine hydrochloride, to a 40-ml. centrifuge tube, add 25 ml. of 0.01 *N* methanolic hydrochloric acid, shake for 10 minutes, and then centrifuge for 5 minutes: a 100-µl. portion of the supernatant liquid so obtained responds to the *Identification test* under *Oxyphencyclimine Hydrochloride*, page 512.

Disintegration, page 878—The disintegration time limit for Oxyphencyclimine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Oxyphencyclimine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Transfer about 50 mg. of NF Oxyphencyclimine Hydrochloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 10.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Weigh and finely powder not less than 20 Oxyphencyclimine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of oxyphencyclimine hydrochloride, to a 100-ml. volumetric flask, add 60 ml. of methanol, and shake mechanically for 15 minutes. Dilute to volume with methanol, mix, and filter, discarding the first 15 ml. of filtrate. Transfer 10.0 ml. of the subsequent filtrate to a 50-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate glass-stoppered 40-ml. centrifuge tubes, and transfer 2.0 ml. of water to a third tube to serve as the blank. To each tube add 3 ml. of water and 1 ml. of 0.25 *N* sodium hydroxide, and heat in a boiling water bath for 10 minutes. Cool, and add 2 ml. of 0.2 *M* ceric sulfate in diluted sulfuric acid (prepared by dissolving 12.6 g. of ceric ammonium sulfate in 50 ml. of water and 3 ml. of sulfuric acid, and diluting to 100 ml. with water). Add 20.0 ml. of isooctane, shake for 15 minutes, allow the layers to separate, and remove the isooctane solution from each tube. Concomitantly determine the absorbances of the isooctane solutions, in 1-cm. cells, at the maximum at about 239 mµ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{20}H_{28}N_2O_3 . HCl$ in the portion of Tablets taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Oxyphencyclimine Tablets in tight, light-resistant containers.

Tablets available—Oxyphencyclimine Hydrochloride Tablets usually available contain the following amount of oxyphencyclimine hydrochloride: 10 mg.

CATEGORY and DOSE—See Oxyphencyclimine Hydrochloride.

Oxytetracycline, Calcium, page 125
Oxytetracycline, Calcium, Oral Suspension, page 125

Ophthalmic Oxytetracycline Hydrochloride

Ophthalmic Oxytetracycline Hydrochloride is a sterile mixture of oxytetracycline hydrochloride with a suitable buffer and/or bacteriostatic agent. It contains not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{22}H_{24}N_2O_9$ (anhydrous oxytetracycline). Ophthalmic Oxytetracycline Hydrochloride conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Ophthalmic Oxytetracycline Hydrochloride in tight, light-resistant containers.

CATEGORY—Antibacterial.

APPLICATION—Topically 1 or 2 drops of a 0.5 percent solution every 2 hours.

Oxytetracycline Injection

Oxytetracycline Injection is a sterile solution of oxytetracycline with or without one or more suitable buffer substances, anesthetics, preservatives, antioxidants, complexing agents, and solvents, in water for injection. It contains an amount of $C_{22}H_{24}N_2O_9 . 2H_2O$ (oxytetracycline) equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{22}H_{24}N_2O_9$ (anhydrous oxytetracycline). Oxytetracycline Injection conforms to the regulations of the federal Food and Drug Administration concerning antibiotic drugs.

Packaging and storage—Preserve Oxytetracycline Injection in single-dose or in multiple-dose containers.

Injections available—Oxytetracycline Injection usually available contains oxytetracycline equivalent to the following amounts of anhydrous oxytetracycline: 50 mg. in 2 ml.; 100 mg. in 2 ml.; 250 mg. in 2 ml.

CATEGORY—Antibacterial.

USUAL DOSE OF OXYTETRACYCLINE—Intramuscular, **250 mg.** four times a day.

USUAL DOSE RANGE—**250** to **500 mg.**

Pancreatin

Pancreatin is a substance containing enzymes, principally amylase, protease, and lipase, obtained from the pancreas of the hog, *Sus scrofa* Linné var. *domesticus* Gray (Fam. *Suidæ*) or of the ox, *Bos taurus* Linné (Fam. *Bovidæ*). Pancreatin converts not less than 25 times its weight of NF Potato Starch Reference Standard into soluble carbohydrates, and not less than 25 times its weight of casein into proteoses. Pancreatin of a higher digestive power may be labeled as a whole-number multiple of the two minimum activities or may be diluted by admixture with lactose, or with sucrose containing not more than 3.25 percent of starch, or with pancreatin of lower digestive power.

Description—Pancreatin occurs as a cream-colored, amorphous powder, having a faint, characteristic, but not offensive odor. Pancreatin changes protein into proteoses and derived substances, and converts starch into dextrins and sugars. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides render it inert. An excess of alkali carbonate also inhibits its action.

Fat—Place 2.0 g. of Pancreatin into a flask of about 50-ml. capacity, add 20 ml. of ether, stopper, and set it aside for several hours, mixing by rotating at frequent intervals. Decant the supernatant ether by means of a guiding rod into a plain filter of about 7 cm. diameter, previously moistened with ether, and collect the filtrate in a tared beaker. Repeat the extraction with a 10-ml. portion of ether, proceeding as directed before, then another portion of 10 ml. of ether, and transfer the ether and the remainder of the Pancreatin to the filter. Allow to drain, evaporate the ether spontaneously, and dry the residue at 105° for 2 hours: the residue of fat weighs not more than 60 mg. (3.0 percent).

Salmonella, page 862—The test for *Salmonella* in Pancreatin is negative.

Assay for amylase activity (*starch diges-*

tive power)—Determine the percentage of moisture in NF Potato Starch Reference Standard by drying about 500 mg., accurately weighed, at 120° for 4 hours. Boil a sufficient amount of water for 10 minutes, and cool to room temperature. Use this water for all dilutions hereinafter specifying water. Thoroughly mix a quantity of the NF Potato Starch Reference Standard, equivalent to 3.75 g. of dry Reference Standard, with 10 ml. of water. Add the mixture, with constant stirring, to 75 ml. of water, previously heated to about 55°, and contained in a tared, 250-ml. beaker. Rinse the remaining starch into the beaker with 10 ml. of water. Heat the mixture to boiling, and boil it gently, with constant stirring, for 5 minutes. Add enough water to make the mixture weigh 100 g., cool the paste to 40°, and place the beaker in a water bath maintained at 40°. Suspend 150 mg. of Pancreatin in 5 ml. of water in a 250-ml. beaker. (Use an inversely proportionate amount of Pancreatin if it is labeled to contain a whole-number multiple of the minimum requirement for digestive activity.) Add the suspension to the starch paste, mixing it well by pouring the mixture from beaker to beaker for 30 seconds, noting the time when the Pancreatin suspension was first added to the paste. Maintain the mixture at a temperature of 40° for exactly 5 minutes. Stir, and at once add 0.1 ml. of this mixture to a previously made mixture of 0.2 ml. of 0.1 *N* iodine and 60 ml. of water, at a temperature of from 23° to 25°, and mix: no blue or violet color is produced.

Assay for protease activity (*Casein digestive power*)—

Casein substrate—Place 1.25 g. of finely powdered casein in a 100-ml. conical flask containing 5 ml. of water, shake to form a suspension, add 10 ml. of 0.1 *N* sodium hydroxide, shake for 1 minute, add 50 ml. of water, and shake for about 1 hour to dissolve the casein. The resulting solution should have a pH about 8. If necessary, adjust the pH to about 8, using 1 *N* sodium hydroxide or 1 *N* hydrochloric acid. Transfer the solution quantitatively to a 100-ml. volumetric flask, dilute to volume with water, and mix. This substrate must be used on the day it is prepared.

Buffer solution—Dissolve 6.8 g. of monobasic potassium phosphate and 1.8 g. of sodium hydroxide in 950 ml. of water in a 1000-ml. volumetric flask, adjust to pH 7.5 ± 0.2, using 0.2 *N* sodium hydroxide, dilute to volume with water, and mix. This solution must be stored in a refrigerator.

Trichloroacetic acid solution—Dissolve 50 g. of trichloroacetic acid in 1000 ml. of water. This solution may be stored at room temperature.

Filter paper—Determine the suitability of the filter paper by filtering a 5-ml. portion of *Trichloroacetic acid solution* through the paper and measuring the absorbance of the filtrate at 280 mμ, using an unfiltered portion of the same *Trichloroacetic acid solution* as the blank: the absorbance is not more than 0.04. If the absorbance is more than 0.04 the filter paper may be washed repeatedly with the *Trichloroacetic acid solution* until the absorbance of the filtrate, determined as above, is not more than 0.04.

Standard test dilution—Add about 100 mg. of NF Pancreatin Reference Standard, accurately weighed, to 100.0 ml. of *Buffer solution*, and mix by shaking intermittently for about 25 minutes at room temperature. Dilute 5.0 ml. of the mixture to 50.0 ml. with *Buffer solution*.

Assay test dilution—Add about 100 mg. of Pancreatin, accurately weighed, to 100.0 ml. of *Buffer solution*, and mix by shaking intermittently for 25 minutes at room temperature. Dilute quantitatively with *Buffer solution* to obtain a dilution that corresponds in activity to the *Standard test dilution*.

Procedure—Label test tubes in duplicate S_1, S_2, and S_3, for the standard series, and U for the sample. Pipet into tubes S_1 2.0 ml., into S_2 and U 1.5 ml., and into S_3 1.0 ml. of *Buffer solution*. Pipet into tubes S_1 1.0 ml., into S_2 1.5 ml., and into S_3 2.0 ml. of the *Standard test dilution*. Pipet into tubes U 1.5 ml. of the *Assay test dilution*. Pipet into 1 tube each of S_1, S_2, S_3, and U 5.0 ml. of *Trichloroacetic acid solution*, and mix. Designate these tubes as S_{1B}, S_{2B}, S_{3B}, and U_B, respectively. Prepare a blank by mixing 3 ml. of *Buffer solution* and 5 ml. of *Trichloroacetic acid solution* in a separate test tube marked B. Place all the tubes in a 40° water bath, insert a glass stirring rod into each tube, and allow for temperature equilibration. At zero time, add to each tube, at timed intervals, 2.0 ml. of the *Casein substrate*, preheated to the bath temperature, and mix. Exactly 60 minutes after the addition of the *Casein substrate* stop the reaction in tubes S_1, S_2, S_3, and U by adding 5.0 ml. of *Trichloroacetic acid solution* at the corresponding time intervals, stir, and remove all the tubes from the bath. Allow to stand for 10 minutes at room temperature for complete protein precipitation, and filter. The filtrates must be free from haze. Determine the absorbance of the filtrates in 1-cm. cells at 280 mμ, with a suitable spectrophotometer, using the filtrate from the blank (tube B) to set the instrument.

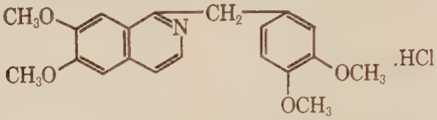
Calculation of potency—Correct the absorbance values for the filtrates from tubes S_1, S_2, and S_3 by subtracting the absorbance values for the filtrates from tubes S_{1B}, S_{2B}, and S_{3B}, respectively, and plot the corrected absorbance values against the corresponding volumes of the *Standard test dilution* used. From the curve, interpolate the corrected absorbance value for the sample ($U - U_B$), and, taking into consideration the dilution factors, calculate the parts of casein digested by 1 part of the Pancreatin taken relative to the Standard, using the casein digestive power of NF Pancreatin Reference Standard stated on the label. One part of Pancreatin digests not less than 25 parts of casein.

Packaging and storage—Preserve Pancreatin in tight containers, preferably at a temperature not above 30°.

Category—Digestive aid.

Usual dose—**500 mg.** to **1 g.**

Papaverine Hydrochloride



6,7-Dimethoxy-1-veratrylisoquinoline Hydrochloride

$C_{20}H_{21}NO_4 . HCl$ Mol. wt. 375.86

Papaverine Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{20}H_{21}NO_4 . HCl$, calculated on the dried basis.

Description—Papaverine Hydrochloride occurs as white crystals or as a white, crystalline powder. It is odorless, and has a slightly bitter taste. It is optically inactive. Its solutions are acid to litmus. It melts at about 220° with decomposition.

Solubility—Papaverine Hydrochloride is soluble in water, and is slightly soluble in alcohol. It is soluble in chloroform, and is practically insoluble in ether.

Identification—

A: A solution of Papaverine Hydrochloride (1 in 50) yields precipitates with mercuric chloride T.S., with iodine T.S., with potassium ferricyanide T.S., and with trinitrophenol T.S.

B: To 10 ml. of a solution of Papaverine Hydrochloride (1 in 100) in a separator add a slight excess of ammonia T.S., and extract with 10 ml. of ether. Wash the separated ether by shaking with 5 ml. of water, and filter the separated ether layer through filter paper moistened with ether. Evaporate the ether solution at a low temperature, and dry the residue at 105° for 2 hours: the papaverine so obtained melts between 145° and 148°, page 814.

C: Dissolve about 1 mg. of Papaverine Hydrochloride in 0.1 ml. of sulfuric acid-formaldehyde T.S.: a colorless or a faintly yellowish green solution is produced, which gradually changes to deep rose and finally becomes brown (distinction from *morphine and codeine,* which give purple or violet colors).

D: A solution of Papaverine Hydrochloride (1 in 50) responds to the tests for *Chloride,* page 808.

pH, page 824—The pH of a solution of Papaverine Hydrochloride (1 in 50) is between 3.0 and 4.5.

Loss on drying, page 814—Dry Papaverine Hydrochloride at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Papaverine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Cryptopine, thebaine, or other organic impurities—Dissolve 50 mg. of Papaverine Hydrochloride in 2 ml. of sulfuric acid in a small test tube: the resulting solution is not more yellow-brown in color than Matching Fluid S (see page 856), and it is not more pink than a standard prepared, in equal volume, by diluting 3.0 ml. of 0.1 *N* potassium permanganate to 1000 ml.

Morphine—Dissolve about 10 mg. of Papaverine Hydrochloride in 10 ml. of water, add a few drops of hydrochloric acid and a few drops of a saturated solution of iodine pentoxide, and shake the solution with 5 ml. of carbon tetrachloride: the carbon tetrachloride layer is not colored violet.

Assay—Dissolve about 700 mg. of Papaverine Hydrochloride, accurately weighed, in 80 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 37.59 mg. of $C_{20}H_{21}NO_4 . HCl$.

Packaging and storage—Preserve Papaverine Hydrochloride in tight, light-resistant containers.

Category—Smooth muscle relaxant.

Usual dose—Oral, **100 mg.**; intramuscular, **30 mg.**

Usual dose range—Oral, **60** to **200 mg.**; intramuscular, **30** to **60 mg.**

Papaverine Hydrochloride Injection

Papaverine Hydrochloride Injection is a sterile solution of papaverine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{20}H_{21}NO_4.HCl$.

Identification—Papaverine Hydrochloride Injection responds to *Identification tests A* and *D* under *Papaverine Hydrochloride*, page 516. The papaverine obtained in the *Assay* melts between 145° and 148°, page 814, and responds to *Identification test C* under *Papaverine Hydrochloride*, page 516.

pH, page 824—The pH of Papaverine Hydrochloride Injection is not below 3.0.

Other requirements—Papaverine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—Transfer to a separator an accurately measured volume of Papaverine Hydrochloride Injection, equivalent to about 120 mg. of papaverine hydrochloride, and add water to make 20 ml. Render alkaline with ammonia T.S., and completely extract the alkaloid by shaking first with 30 ml., then with successive 15-ml. portions of chloroform. Wash the combined chloroform extracts with 10 ml. of water, then filter the chloroform solution through a filter paper moistened with chloroform, and wash the separator and the filter with two 5-ml. portions of chloroform. Evaporate the chloroform solution on a steam bath to about 2 ml. with the aid of a current of air, add 10 ml. of alcohol, evaporate on the steam bath to dryness, and dry at 105° for 2 hours. The weight of the papaverine so obtained, multiplied by 1.107, represents the weight of $C_{20}H_{21}NO_4.HCl$.

Packaging and storage—Preserve Papaverine Hydrochloride Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injections available—Papaverine Hydrochloride Injection usually available contains the following amounts of papaverine hydrochloride: 30 mg. in 1 ml.; 60 mg. in 2 ml.; 300 mg. in 10 ml.

CATEGORY and DOSE—See Papaverine Hydrochloride.

Papaverine Hydrochloride Tablets

Papaverine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{20}H_{21}NO_4.HCl$.

Identification—

A: The filtered extract of powdered Papaverine Hydrochloride Tablets obtained in the *Assay* responds to *Identification tests A* and *D* under *Papaverine Hydrochloride*, page 516.

B: The papaverine obtained in the *Assay* melts between 145° and 148°, page 814, and responds to *Identification test C* under *Papaverine Hydrochloride*, page 516.

Disintegration, page 878—The disintegration time limit for Papaverine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Papaverine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following procedure: Quantitatively transfer a finely powdered tablet to a 250-ml. volumetric flask, add 50 ml. of water and 3 ml. of hydrochloric acid, mix, and allow to stand for 15 minutes with occasional agitation. Dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with water to provide a solution containing approximately 2.4 mcg. of papaverine hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a standard solution of NF Papaverine Hydrochloride, in the same medium, at a concentration of about 2.4 mcg. per ml., in 1-cm. cells, at the maximum at about 250 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{20}H_{21}NO_4.HCl$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of papaverine hydrochloride, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of the sample solution based on the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the standard solution.

Assay—Weigh and finely powder not less than 20 Papaverine Hydrochloride Tablets. Weigh accurately a portion of the powder, equivalent to about 300 mg. of papaverine hydrochloride, transfer to a 100-ml. volumetric flask, and add dilute sulfuric acid (11.4 in 1000) to volume.

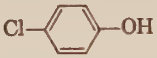
Mix the solution, and allow to stand overnight. Shake well, and filter through a dry filter, discarding the first 20 ml. of filtrate. Pipet a portion of the subsequent filtrate, equivalent to about 100 mg. of papaverine hydrochloride, into a 125-ml. separator, and add stronger ammonia water until the solution is distinctly alkaline. Extract the alkaloid with five 25-ml. portions of chloroform, combine the extracts in a second separator, and wash the combined extracts with 10 ml. of water containing 0.5 ml. of stronger ammonia water. Allow the mixture to separate, and filter the chloroform layer through a dry filter into a dry, tared, 150-ml. beaker. Extract the alkaline wash water with two 10-ml. portions of chloroform, passing the chloroform through the filter. Wash the filter well with chloroform, evaporate the combined chloroform filtrate on a steam bath to about 2 ml., with the aid of a current of air, add 10 ml. of alcohol, evaporate on the steam bath to dryness, and dry at 105° for 2 hours. The weight of the papaverine so obtained, multiplied by 1.107, represents the weight of $C_{20}H_{21}NO_4.HCl$ in the portion of the filtrate taken.

Packaging and storage—Preserve Papaverine Hydrochloride Tablets in tight containers.

Tablets available—Papaverine Hydrochloride Tablets usually available contain the following amounts of papaverine hydrochloride: 30, 60, 100, and 200 mg.

CATEGORY and DOSE—See Papaverine Hydrochloride.

Parachlorophenol



p-Chlorophenol

C_6H_5ClO Mol. wt. 128.56

Parachlorophenol contains not less than 99.0 percent and not more than 100.5 percent of C_6H_5ClO.

Description—Parachlorophenol occurs as white or pink crystals, having a characteristic phenolic odor. When undiluted, it whitens and cauterizes the skin and mucous membranes. Parachlorophenol melts at about 42°.

Solubility—Parachlorophenol is very soluble in alcohol, in glycerin, in chloroform, in ether, and in fixed and volatile oils. It is soluble in petrolatum. It is sparingly soluble in water and in liquid petrolatum.

Identification—

A: To a solution of Parachlorophenol (1 in 100) add bromine T.S. dropwise: a white precipitate forms which at first redissolves, but becomes permanent as an excess of the reagent is added.

B: Add 1 drop of ferric chloride T.S. to 10 ml. of a solution of Parachlorophenol (1 in 100): the solution acquires a violet-blue color.

C: Heat a few crystals of Parachlorophenol, held on a copper wire, in the edge of a nonluminous flame: a green color is imparted to the flame.

D: To a mixture of 1 g. of Parachlorophenol and 5 ml. of sodium hydroxide solution (1 in 3) add 1.5 g. of monochloroacetic acid. Shake well and heat on a steam bath for 1 hour. Cool, dilute with 15 ml. of water, and acidify with hydrochloric acid. Transfer to a separator and extract with 50 ml. of ether. Wash the ether solution with 10 ml. of cold water, then extract the ether solution with 25 ml. of sodium carbonate solution (1 in 20). Acidify the solution with hydrochloric acid, collect the resulting precipitate on a filter, and recrystallize it from hot water: the resulting parachlorophenoxyacetic acid melts at about 155°, page 814.

Congealing temperature, page 794—Parachlorophenol congeals between 42° and 44°.

Nonvolatile residue—Heat about 1 g. of Parachlorophenol, accurately weighed, in a tared container, on a steam bath until it is volatilized, and dry at 105° for 1 hour: not more than 0.1 percent of residue remains.

Clarity and reaction of solution—A solution of Parachlorophenol (1 in 100) is clear and is acid to litmus.

Chloride—Acidify 10 ml. of a solution of Parachlorophenol (1 in 100) with diluted nitric acid, and add a few drops of silver nitrate T.S.: no turbidity or opalescence is produced.

Assay—Dissolve about 1 g. of Parachlorophenol, accurately weighed, in sufficient water to make 500.0 ml. Transfer a 25.0-ml. portion of the solution to an iodine flask, cool to about 4° in an ice bath and add 20.0 ml. of 0.1 *N* bromine. Add 5 ml. of hydrochloric acid and immediately insert the stopper. Keep the flask at 4° during 30 minutes, shaking at frequent intervals. Allow it to stand for 15 minutes, remove the stopper just sufficiently to introduce quickly 5 ml. of potassium iodide solution (1 in 5), being careful that no bromine vapor escapes, and at once stopper the flask. Shake thoroughly, remove the stopper, and rinse it and the neck of the flask with a little water, so that the washings may flow into the flask. Shake the mixture well, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* bromine is equivalent to 3.214 mg. of C_6H_5ClO.

Packaging and storage—Preserve Parachlorophenol in tight, light-resistant containers.

CATEGORY—Local anti-infective (dental).

Parachlorophenol, Camphorated, page 132

Paraffin

Paraffin is a purified mixture of solid hydrocarbons obtained from petroleum.

Description—Paraffin occurs as a colorless or white, more or less translucent mass showing a crystalline structure. It is without odor or taste, and is slightly greasy to the touch.

Solubility—Paraffin is freely soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils. It is slightly soluble in dehydrated alcohol, and is insoluble in water and in alcohol.

Identification—

A: When strongly heated, Paraffin ignites with a luminous flame and deposits carbon.

B: Heat about 500 mg. of Paraffin in a dry test tube with an equal weight of sulfur: the mixture evolves hydrogen sulfide, and becomes black due to the liberation of carbon.

Congealing temperature, page 794—Paraffin congeals between 47° and 65°.

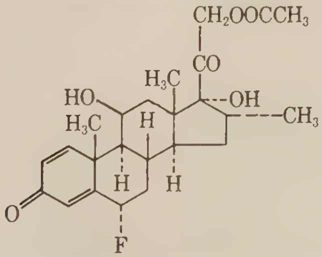
Reaction—Shake melted Paraffin with an equal volume of hot alcohol previously neutralized to litmus paper: the separated alcohol is neutral to litmus paper.

Readily carbonizable substances—Use a clean, dry, heat-resistant, glass-stoppered test tube, 140 mm. ± 3 mm. in length and 14 mm. ± 1 mm. in diameter, with a capacity of 16 ml. ± 1 ml. when the stopper is inserted, and calibrated at the 5-ml. and 10-ml. liquid levels. Place in the test tube 5 ml. of Paraffin, at a temperature just above the melting point, add 5 ml. of sulfuric acid containing 94.5 percent to 94.9 percent of H_2SO_4, and heat in a water bath at 70° for 10 minutes. When 5 minutes have elapsed, and at each successive minute thereafter, remove the tube from the bath, place a finger over the stopper, and give the tube 3 vigorous vertical shakes over an amplitude of about 12 cm., returning the tube to the bath within 3 seconds after the time when it was removed therefrom. At the end of 10 minutes from the time the tube was placed in the bath, the acid has no more color than a mixture of 3 ml. of ferric chloride C.S., 1.5 ml. of cobaltous chloride C.S., and 0.5 ml. of cupric sulfate C.S., overlaid with 5 ml. of mineral oil. If the sulfuric acid remains dispersed in the molten paraffin, the color of the emulsion is not darker than that of the standard mixture when shaken vigorously.

Packaging and storage—Preserve Paraffin in well-closed containers and avoid exposure to temperatures above 40°.

CATEGORY—Stiffening agent.

Paramethasone Acetate



6α-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-Acetate

$C_{24}H_{31}FO_6$ Mol. wt. 434.51

Paramethasone Acetate contains not less than 95.0 percent and not more than 101.0 percent of $C_{24}H_{31}FO_6$, calculated on the dried basis.

Description—Paramethasone Acetate occurs as a fluffy, practically white, odorless, crystalline powder. When tested by the method under *Class Ia*, page 815, it melts at about 240° with decomposition.

Solubility—Paramethasone Acetate is insoluble in water. It is soluble in chloroform, in ether, and in methanol.

Identification—

A: Line the inside of a chromatographic chamber suitable for descending chromatography (see page 789) with filter paper. Fill the solvent trough with a saturated solution of formamide in benzene to serve as the mobile phase, and also place a sufficient quantity of the same liquid in the bottom of the chamber to permit the liner to be in contact with it. Allow the chamber to equilibrate overnight. Prepare a strip of 10 × 45-cm. filter paper, draw a line across the narrow dimension about 6 cm. from one end, and mark two points for application of solutions along this line about 2.5 cm. from each edge of the paper. Immerse the paper in a 2:1 mixture of acetone-formamide, and blot thoroughly. Prepare a solution of Paramethasone Acetate in a 1:1 mixture of chloroform-methanol containing 10 mg. per ml. Spot 10 µl. of this solution and 10 µl. of a solution of NF Paramethasone Acetate Reference Standard in the same medium containing 10 mg. per ml. Suspend the strip in the developing chamber, and allow to develop until the solvent front is within 3 to 4 cm. of the bottom of the strip. Remove the strip, mark the solvent front, and dry the strip in air for 10 to 15 minutes, or until the benzene has evaporated. Observe the chromatogram under shortwave ultraviolet light, and mark with a soft lead pencil all of the quenching and fluorescing spots. Continue drying the strip overnight, and then spray the strip with a solution prepared by mixing 10 ml. of blue tetrazolium solution (1 in 500) and 5 ml. of sodium hydroxide solution (1 in 10). Circle all purplish spots while the strip is still wet, and then dry in air: the main spot obtained from the sample corresponds in R_f value, pattern, and intensity of zones to that obtained from the Reference Standard solution.

B: Heat to boiling in a water bath about 50 mg. of Paramethasone Acetate with 2 ml. of alcoholic potassium hydroxide T.S., cool, add 2 ml. of dilute sulfuric acid (1 in 3.5), and boil gently for 1 minute: the odor of ethyl acetate is perceptible.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Paramethasone Acetate, previously dried in vacuum at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Paramethasone Acetate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Paramethasone Acetate in methanol exhibits maxima and minima at the same wavelengths as that of NF Paramethasone Acetate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance at about 242 mµ, do not differ by more than 4 percent.

Specific rotation, page 822—The specific rotation of Paramethasone Acetate, previously dried in vacuum at 105° for 4 hours, determined in a solution in chloroform containing 100 mg. of Paramethasone Acetate in each 10 ml., is between +67° and +77°.

X-ray diffraction, page 902—The X-ray diffraction pattern of Paramethasone Acetate conforms to either one or a mixture of the patterns described by the following data:

Form A		Form B	
d	I/I_1	*d*	I/I_1
12.09	10	11.62	20
8.42	20	7.80	8
7.78	10	7.13	10
6.41	100	6.50	60
5.65	100	5.98	100
5.50	10	5.63	70
5.18	2	5.30	100
4.59	30	4.85	60
4.41	20	4.65	60
4.24	40	4.43	8
3.93	20	4.30	2
3.64	30b	3.93	60
3.48	15	3.72	6
3.27	20	3.58	4
3.12	30	3.45	4
3.03	8	3.26	10
2.90	2	3.09	10
2.82	8	2.96	10
2.70	10	2.88	10
2.61	8	2.81	6b
2.51	10	2.66	8b
2.35	2	2.55	6
2.29	8	2.48	6b
2.24	6	2.38	10
2.11	4	2.30	6
2.08	2	2.26	8
2.04	4	2.19	6
2.00	4	2.11	10
1.95	1	2.04	8
1.92	4	1.99	10
1.87	2		
1.84	2		
1.82	1		

Loss on drying, page 814—Dry Paramethasone Acetate in vacuum at 105° for 4 hours: it loses not more than 1 percent of its weight.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Paramethasone Acetate Reference Standard to prepare a solution containing approximately 10 mg. per ml.

Test preparation—Weigh accurately about 50 mg. of Paramethasone Acetate, previously dried at 105° for 4 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 5.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, applying 10 µl. each of the *Test Preparation* and of the *Standard Preparation* to the chromatographic plate, and using a solvent system consisting of benzene and ethyl acetate (40:60). Determine the absorbances at the maximum at about 242 mµ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 5 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Paramethasone Acetate taken: not more than 3 percent is found.

Assay—

Isoniazid reagent—Dissolve 250 mg. of isonicotinic acid hydrazide in 300 ml. of methanol, slowly add 0.5 ml. of hydrochloric acid, then dilute to 500 ml. with methanol, and mix.

Standard preparation—Transfer about 20 mg. of NF Paramethasone Acetate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix.

Assay preparation—Transfer about 20 mg. of Paramethasone Acetate, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix.

Procedure—Transfer 2.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of methanol to serve as the blank to separate 25-ml. volumetric flasks, add 10.0 ml. of *Isoniazid reagent* to each flask, and heat at 53° to 57° in a water bath for 45 minutes, swirling occasionally. Cool, dilute each flask to volume with methanol, mix, and allow to stand for 5 minutes. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 405 mµ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{24}H_{31}FO_6$ in the Paramethasone Acetate taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Paramethasone Acetate in tight containers.

Category—Glucocorticoid.

Usual dose range—Initial, **4** to **12 mg.** daily in three or four divided doses; maintenance, **1** to **8 mg.** daily in divided doses.

Paramethasone Acetate Tablets

Paramethasone Acetate Tablets contain not less than 85.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{31}FO_6$.

Identification—The infrared absorption spectrum of the *Assay preparation*, prepared as directed in the *Assay*, exhibits maxima only at the same wavelengths as that of the *Standard preparation*, prepared as directed in the *Assay*.

Disintegration, page 878—The disintegration time limit for Paramethasone Acetate Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Paramethasone Acetate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 50-ml. volumetric flask, add 25 ml. of chloroform, and shake mechanically for 15 minutes. Dilute to volume with chloroform, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with chloroform to provide a solution containing approximately 20 mcg. of paramethasone acetate per ml. Transfer 10.0 ml. of this solution and of a solution of NF Paramethasone Acetate Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., to separate 25-ml. volumetric flasks, and transfer 10 ml. of chloroform to a third flask to serve as the blank. To each flask add 3.0 ml. of a 1 in 4000 solution of blue tetrazolium in alcohol and 5.0 ml. of dilute (1 in 20 with alcohol) tetramethylammonium hydroxide T.S., mixing after each addition. Exactly 15 minutes after the addition of the last reagent, add 1 ml. of glacial acetic acid to each flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of the solutions in 1-cm. cells, at the maximum at about 525 mµ, with a suitable spectrophotometer, using the blank to set the instrument. Calculate the quantity, in mg., of $C_{24}H_{31}FO_6$ in the Tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of paramethasone acetate, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—

Standard preparation—Transfer about 6 mg. of NF Paramethasone Acetate Reference Standard, accurately weighed, to a separator containing 15 ml. of water, and continue as directed under *Assay preparation*, beginning with "... add 3 drops of hydrochloric acid. ..."

Assay preparation—Weigh and finely powder not less than 20 Paramethasone Acetate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 6 mg. of paramethasone acetate, to a separator containing 15 ml. of water, add 3 drops of hydrochloric acid, and heat on a steam bath for 5 minutes, mixing frequently. Cool the separator to room temperature, add 4 drops of sodium hydroxide solution (1 in 2), and immediately extract with four 25-ml. portions of chloroform. Filter the extracts through anhydrous sodium sulfate, collecting the extracts in a beaker. (Caution—Do not allow the filter paper to extend above the top of the funnel.) Rinse the filter with several small portions of chloroform, add the rinsings to the beaker, and evaporate the chloroform on a steam bath with the aid of a current of air until about 3 ml. remain. Quantitatively transfer the remaining liquid, with the aid of several small portions of chloroform to a 10-ml. glass-stoppered conical flask, and evaporate to dryness on a steam bath with the aid of a current of air. Add 2.0 ml. of chloroform to the flask, stopper, and mix to dissolve the residue.

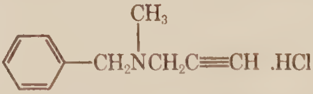
Procedure—Concomitantly determine the absorbances of the solutions in 1-mm. cells at the maximum at 6.04 μ, with a suitable infrared spectrophotometer, using chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{24}H_{31}FO_6$ in the portion of the Tablets taken by the formula $W \times (A_U/A_S)$, in which W is the exact weight, in mg., of NF Paramethasone Acetate Reference Standard used in preparing the *Standard preparation*.

Packaging and storage—Preserve Paramethasone Acetate Tablets in well-closed containers.

Tablets available—Paramethasone Acetate Tablets usually available contain the following amounts of paramethasone acetate: 1 and 2 mg.

CATEGORY and DOSE—See Paramethasone Acetate.

Pargyline Hydrochloride*



N-Methyl-*N*-2-propynylbenzylamine Hydrochloride

$C_{11}H_{13}N.HCl$ Mol. wt. 195.69

Pargyline Hydrochloride contains not less than 98.0 percent and not more than 101.0 percent of $C_{11}H_{13}N.HCl$, calculated on the anhydrous basis.

Description—Pargyline Hydrochloride occurs as a white or practically white, crystalline powder having a slight odor. It sublimes slowly at elevated temperatures.

Solubility—Pargyline Hydrochloride is very soluble in water, and is freely soluble in alcohol and in chloroform. It is very slightly soluble in acetone and in benzene.

Identification—

A: Dissolve 1.5 g. of cupric chloride and 3 g. of ammonium chloride in 20 ml. of stronger ammonia water and dilute to 50 ml. with water. Just prior to use, mix one volume of this solution with two volumes of hydroxylamine hydrochloride solution (1 in 10), and then add 3 drops of this solution to 100 mg. of Pargyline Hydrochloride dissolved in 1 ml. of water: a copious, pale yellow precipitate is formed.

B: Dissolve about 50 mg. of Pargyline Hydrochloride in 3 ml. of water, add ammonia T.S. until the solution is alkaline, and filter. Acidify the filtrate with diluted nitric acid, and add 1 ml. of silver nitrate T.S.: a white precipitate, which is insoluble in diluted nitric acid but soluble in ammonia T.S., is formed.

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* Patented. See notice, page ii.

Melting range, page 814—Pargyline Hydrochloride melts between 158° and 162°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Pargyline Hydrochloride, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Pargyline Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 1000 solution of Pargyline Hydrochloride in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Pargyline Hydrochloride Reference Standard, similarly measured.

Water, page 900—Determine the water content of Pargyline Hydrochloride by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Pargyline Hydrochloride yields not more than 0.2 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Pargyline Hydrochloride in 20 ml. of water, add 2 ml. of diluted acetic acid, and dilute with water to 25 ml.: the heavy metals limit for Pargyline Hydrochloride is 20 parts per million.

Assay—Dissolve about 200 mg. of Pargyline Hydrochloride, accurately weighed, in 90 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 19.57 mg. of $C_{11}H_{13}N \cdot HCl$.

Packaging and storage—Preserve Pargyline Hydrochloride in tight containers.

CATEGORY—Antihypertensive.

USUAL DOSE—Initial, **10** to **25 mg.** once daily, then increase daily dose in increments of 10-mg. once a week until the desired response is obtained.

Pargyline Hydrochloride Tablets

Pargyline Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{13}N \cdot HCl$.

Identification—Dissolve a quantity of powdered Pargyline Hydrochloride Tablets, equivalent to about 10 mg. of pargyline hydrochloride, in 2 ml. of water, and filter: the filtrate responds to *Identification test A* under *Pargyline Hydrochloride,* page 522.

Disintegration, page 878—The disintegration time limit for Pargyline Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Pargyline Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

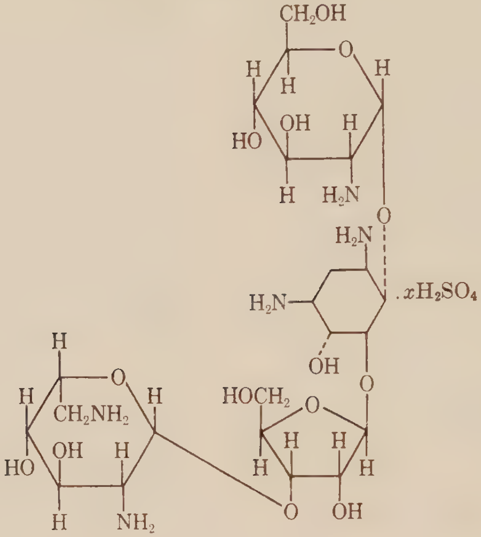
Assay—Weigh and finely powder not less than 20 Pargyline Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg. of pargyline hydrochloride, to a separator, add about 30 ml. of water, make distinctly alkaline (pH 10) with sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform. Wash the combined extracts with 15 ml. of water, discard the water layer, and filter the chloroform layer through anhydrous sodium sulfate supported on a pledget of glass wool, receiving the filtrate in a beaker. Rinse the separator and the anhydrous sodium sulfate with several small portions of chloroform, collect the rinsings in the beaker, add 25 ml. of acetonitrile, and titrate with 0.1 *N* perchloric acid in dioxane, determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 19.57 mg. of $C_{11}H_{13}N \cdot HCl$.

Packaging and storage—Preserve Pargyline Hydrochloride Tablets in well-closed containers.

Tablets available—Pargyline Hydrochloride Tablets usually available contain the following amounts of pargyline hydrochloride: 10, 25, and 50 mg.

CATEGORY and DOSE—See Pargyline Hydrochloride.

Paromomycin Sulfate*



$C_{23}H_{45}N_5O_{14}.xH_2SO_4$ Mol. wt. (base) 615.64

Paromomycin Sulfate is the sulfate of an antibiotic substance or substances produced by the growth of *Streptomyces rimosus* var. *paromomycinus*, or by other means. It has a potency equivalent to not less than 675 mcg. of paromomycin base per mg., calculated on the anhydrous basis. Paromomycin Sulfate conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Paromomycin Sulfate occurs as an off-white to light yellow amorphous powder. It is odorless or practically odorless and is very hygroscopic.

Solubility—Paromomycin Sulfate is very soluble in water. It is insoluble in alcohol, in chloroform, and in ether.

Packaging and storage—Preserve Paromomycin Sulfate in tight containers.

Category—Antiamebic.

Usual dose—The equivalent of **500 mg.** of paromomycin every 6 hours taken with meals.

Usual dose range—**500 mg.** to **1 g.** of paromomycin.

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* Patented. See notice, page ii.

Paromomycin Sulfate Capsules

Paromomycin Sulfate Capsules contain not less than 90.0 percent and not more than 125.0 percent of the labeled amount of paromomycin. Paromomycin Sulfate Capsules conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Paromomycin Sulfate Capsules in tight containers.

Capsules available—Paromomycin Sulfate Capsules usually available contain paromomycin sulfate equivalent to the following amount of paromomycin: 250 mg.

Category and Dose—See Paromomycin Sulfate.

Pectin

Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.

Pectin yields not less than 6.7 percent of $—OCH_3$(methoxy groups) and not less than 74.0 percent of $C_6H_{10}O_7$ (galacturonic acid), calculated on the dried basis.

Pectin may be standardized to the convenient "150 jelly grade" by addition of dextrose or other sugars, and it may contain sodium citrate or other buffer salts.

Description—Pectin occurs as a coarse or fine powder, yellowish white in color, almost odorless, and with a mucilaginous taste.

Solubility—Pectin is almost completely soluble in 20 parts of water, forming a viscous, opalescent, colloidal solution which flows readily and is acid to litmus. It is practically insoluble in alcohol or in diluted alcohol, and in other organic solvents. Pectin dissolves in water more readily if first moistened with alcohol, glycerin, or simple syrup, or if first mixed with 3 or more parts of sucrose.

Identification—

A: Heat 1 g. of Pectin with 9 ml. of water on a steam bath until a solution is formed, replacing water lost by evaporation: it yields a stiff gel upon cooling.

B: To a solution of Pectin (1 in 100) add an equal volume of alcohol: a translucent, gelatinous precipitate is formed (*difference from most gums*).

C: To 10 ml. of a solution of Pectin (1 in 100) add 1 ml. of thorium nitrate T.S., stir, and allow to stand for 2 minutes: a stable precipitate or gel forms (*difference from gums*).

D: To 5 ml. of a solution of Pectin (1 in 100) add 1 ml. of a solution of potassium hydroxide (1 in 50) and allow to stand at room temperature for 15 minutes: a transparent gel or semi-gel forms (*difference from tragacanth*).

E: Acidify the gel from the preceding test with diluted hydrochloric acid and shake well: a voluminous, colorless, gelatinous precipitate forms, which upon boiling becomes white and flocculent (*pectic acid*).

Loss on drying, page 814—Dry Pectin at 105° for 2 hours: it loses not more than 10 percent of its weight.

Arsenic—A *Test Preparation* prepared with 3.33 g. of Pectin, as directed for organic compounds, meets the requirements of the *Arsenic Test*, page 777 (3 parts per million As).

Lead—Add 2.0 g. of Pectin to 20 ml. of nitric acid in a 250-ml. conical flask, mix well, and heat the contents carefully until the Pectin is dissolved. Continue the heating until the volume is reduced to about 7 ml. Cool rapidly to room temperature, transfer to a 100-ml. volumetric flask, and dilute to volume with water. A 50.0-ml. portion of this solution contains not more than 5 mcg. of lead (corresponding to not more than 5 parts per million) when tested according to the *Lead Limit Test*, page 813, using 15 ml. of ammonium citrate solution, 3 ml. of potassium cyanide solution, and 0.5 ml. of hydroxylamine hydrochloride solution. After the first dithizone extractions, wash the combined chloroform layers with 5 ml. of water, discarding the water layer and continuing in the usual manner by extracting with 20 ml. of 1 percent nitric acid.

Salmonella, page 862—The test for *Salmonella* in Pectin is negative.

Starch—Boil a 1 percent solution of Pectin, cool, and add a few drops of iodine T.S.; not even a transient blue color is produced.

Assay for methoxy groups—Transfer 5.00 g. of Pectin to a suitable beaker and stir for 10 minutes with a mixture of 5 ml. of hydrochloric acid and 100 ml. of 60 percent alcohol. Transfer to a sintered-glass filter (30- to 60-ml. crucible or Büchner type, coarse) and wash with six 15-ml. portions of the hydrochloric acid-60 percent alcohol mixture, followed by 60 percent alcohol until the filtrate is free of chlorides. Finally wash with 20 ml. of alcohol and dry for 1 hour at 105°, cool, and weigh. Transfer exactly one-tenth of the total net weight of the dried sample (representing 500 mg. of the original unwashed sample) to a 250-ml. conical flask and moisten the sample with 2 ml. of alcohol. Add 100 ml. of carbon dioxide-free water, stopper, and swirl occasionally until the Pectin is completely dissolved. Add 5 drops of phenolphthalein T.S., titrate with 0.5 N sodium hydroxide, and record the results as the *initial titer*. Add 20.0 ml. of 0.5 N sodium hydroxide, stopper, shake vigorously, and let stand for 15 minutes. Add 20.0 ml. of 0.5 N hydrochloric acid and shake until the pink color disappears. Add 3 drops of phenolphthalein T.S., and titrate with 0.5 N sodium hydroxide to a faint pink color which persists after vigorous shaking: record this value as the *saponification titer*. Each ml. of 0.5 N sodium hydroxide used in the *saponification titer* is equivalent to 15.52 mg. of —OCH_3.

Assay for galacturonic acid—Each ml. of 0.5 *N* sodium hydroxide used in the total titration (the *initial titer* added to the *saponification titer*) in the *Assay for methoxy groups* is equivalent to 97.07 mg. of $C_6H_{10}O_7$.

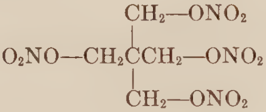
Packaging and storage—Preserve Pectin in tight containers.

Labeling—Label Pectin to indicate whether it is pure pectin or "150 jelly grade" pectin.

Category—Protectant.

Pectin with Kaolin Mixture, page 388
Penicillin G, Sodium, page 653
Penicillin G, Sodium, for Injection, page 654

Diluted Pentaerythritol Tetranitrate



$$\begin{array}{c} \mathrm{CH_2{-}ONO_2} \\ | \\ \mathrm{O_2NO{-}CH_2CCH_2{-}ONO_2} \\ | \\ \mathrm{CH_2{-}ONO_2} \end{array}$$

2,2-Bis(hydroxymethyl)-1,3-propanediol Tetranitrate

$C_5H_8N_4O_{12}$ Mol. wt. 316.14

Diluted Pentaerythritol Tetranitrate is a dry mixture of pentaerythritol tetranitrate ($C_5H_8N_4O_{12}$) with lactose or mannitol or other suitable inert excipients, to permit safe handling and compliance with federal Interstate Commerce Commission regulations pertaining to interstate shipment. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_5H_8N_4O_{12}$.

Caution: Undiluted pentaerythritol tetranitrate is a powerful explosive, and proper precautions must be taken in handling. It can be exploded by percussion or by excessive heat. Only extremely small amounts should be isolated.

Description—Diluted Pentaerythritol Tetranitrate occurs as a white to ivory colored powder having a faint, mild odor.

Solubility—Undiluted pentaerythritol tetranitrate is soluble in acetone, slightly soluble in alcohol and in ether, and practically insoluble in water.

Identification—Transfer to a medium-porosity sintered-glass filter an amount of Diluted Pentaerythritol Tetranitrate, equivalent to not more than 10 mg. of pentaerythritol tetranitrate, and pass several small portions of dry acetone through the sample to extract the pentaerythritol tetranitrate. Evaporate the combined extracts in a beaker at a temperature not exceeding 60°, with the aid of a gentle current of air, and dry the residue at 60° for 4 hours: the crystals of pentaerythritol tetranitrate so obtained melt between 138° and 143°.

Assay—

Standard preparation—Transfer about 130 mg. of potassium nitrate, previously dried at 105° for 4 hours and accurately weighed, to a 200-ml. volumetric flask, dissolve in 3 ml. of water, dilute to volume with glacial acetic acid, and mix.

Assay preparation—Transfer an accurately weighed amount of Diluted Pentaerythritol Tetranitrate, equivalent to about 50 mg. of pentaerythritol tetranitrate, to a medium-porosity sintered-glass filter, and extract the pentaerythritol by passing ten 5-ml. portions of dry acetone through the mixture, collecting the filtrates in a suction flask. Allow each portion to drain through the sample for 3 minutes, and then apply suction to draw the free liquid through the filter, removing the suction as soon as the free liquid has been aspirated. Quantitatively transfer the combined filtrates to a beaker, and wash the flask and stem of the filter with three 5-ml. portions of acetone, adding the washings to the filtrate. Evaporate the combined filtrate and washings nearly to dryness at a temperature not exceeding 35°, with the aid of a current of air. Dissolve the residue in glacial acetic acid, quantitatively transfer to a 100-ml. volumetric flask, dilute to volume with glacial acetic acid, and mix.

Procedure—Transfer 1.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 100-ml. volumetric flasks. To each flask add 2 ml. of phenoldisulfonic acid T.S., mix, and allow to stand for 5 minutes. Add to each flask 25 ml. of water and 20 ml. of ammonia T.S., cool, dilute to volume with water, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 409 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_5H_8N_4O_{12}$ in the Diluted Pentaerythritol Tetranitrate taken by the formula $0.1C \times 0.7817 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of potassium nitrate in the *Standard preparation*, and 0.7817 is an equivalence factor relating potassium nitrate to pentaerythritol tetranitrate.

Packaging and storage—Preserve Diluted Pentaerythritol Tetranitrate in tight containers, and avoid exposure to excessive heat.

Concentrations available—Diluted Pentaerythritol Tetranitrate usually available contains from 7 to 35 percent of pentaerythritol tetranitrate.

CATEGORY—Vasodilator.

USUAL DOSE—**10 mg.** of pentaerythritol tetranitrate three or four times a day.

USUAL DOSE RANGE—**10** to **20 mg.** of pentaerythritol tetranitrate.

Pentaerythritol Tetranitrate Tablets

Pentaerythritol Tetranitrate Tablets are prepared from diluted pentaerythritol tetranitrate. They contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_5H_8N_4O_{12}$.

Caution: Undiluted pentaerythritol tetranitrate is a powerful explosive, and proper precautions must be taken in handling. It can be exploded by percussion or by excessive heat. Only extremely small amounts should be isolated.

Identification—Extract a portion of finely powdered Pentaerythritol Tetranitrate Tablets, equivalent to about 10 mg. of pentaerythritol tetranitrate, with several small portions of petroleum ether, and discard the extracts. Dry the residue in air until the odor of petroleum ether is no longer perceptible, extract the residue with about 10 ml. of acetone, and filter. Evaporate the filtrate to dryness at a temperature not exceeding 60°, with the aid of a gentle current of air, and then dry the residue at 60° for 4 hours: the crystals of pentaerythritol tetranitrate so obtained melt between 138° and 143°.

Disintegration, page 878—The disintegration time limit for Pentaerythritol Tetranitrate Tablets is 10 minutes.

Content uniformity, *Method I*, page 799—Pentaerythritol Tetranitrate Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Diluted Pentaerythritol Tetranitrate*, page 526.

Assay preparation—Weigh and finely powder not less than 20 Pentaerythritol Tetranitrate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of pentaerythritol tetranitrate, to a 100-ml. volumetric flask, add 50 ml. of glacial acetic acid, and heat on a steam bath for 15 minutes, swirling occasionally. Cool, dilute to volume with glacial acetic acid, and mix.

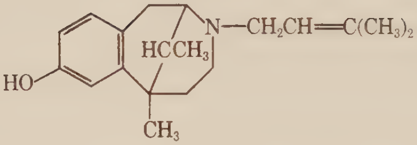
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Diluted Pentaerythritol Tetranitrate*, page 526. Calculate the quantity, in mg., of $C_5H_8N_4O_{12}$ in the portion of Tablets taken by the formula $0.1C \times 0.7817 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of potassium nitrate in the *Standard preparation*, and 0.7817 is an equivalence factor relating potassium nitrate and pentaerythritol tetranitrate.

Packaging and storage—Preserve Pentaerythritol Tetranitrate Tablets in tight containers.

Tablets available—Pentaerythritol Tetranitrate Tablets usually available contain diluted pentaerythritol tetranitrate equivalent to the following amounts of pentaerythritol tetranitrate: 10 and 20 mg.

CATEGORY and DOSE—See Diluted Pentaerythritol Tetranitrate.

Pentazocine*



1,2,3,4,5,6-Hexahydro-*cis*-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol

$C_{19}H_{27}NO$ Mol. wt. 285.43

Pentazocine contains not less than 98.0 percent and not more than 101.5 percent of $C_{19}H_{27}NO$, calculated on the dried basis.

Description—Pentazocine occurs as a white or very pale tan colored powder.

Solubility—Pentazocine is practically insoluble in water and is sparingly soluble in benzene and in ethyl acetate. It is freely soluble in chloroform and is soluble in alcohol, in acetone, and in ether.

Identification—

A: Mix about 1 mg. of Pentazocine with 0.5 ml. of a 1 in 200 solution of molybdic acid in sulfuric acid: an intense blue color is produced, changing on standing to blue-green, then green, and finally yellow-green (*distinction from morphine which gives an intense purple color, changing to green on standing*).

B: Dissolve about 5 mg. of Pentazocine in 5 ml. of sulfuric acid, add 1 drop of ferric chloride T.S., mix, and heat in a boiling water bath for 2 minutes: a yellow color is produced in cold solution and a slightly deeper yellow after heating. Add 1 drop of nitric acid, and mix: the color remains yellow (*distinction from morphine, codeine, and ethylmorphine which produce a blue color when heated and change to a dark reddish brown with the addition of nitric acid*).

Melting range, *Class Ia,* page 815—Pentazocine melts, with slight darkening, between 147° and 158°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Pentazocine, previously dried to constant weight in vacuum at 60°, exhibits maxima only at the same wavelengths as that of NF Pentazocine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 10,000 solution of Pentazocine in 0.01 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Pentazocine Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance occurring at about 278 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Pentazocine to constant weight in vacuum, maintaining the pressure below 5 mm. of mercury, at 60°; it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Pentazocine yields not more than 0.2 percent of residue on ignition.

Assay—Dissolve about 500 mg. of Pentazocine, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 28.54 mg. of $C_{19}H_{27}NO$.

Packaging and storage—Preserve Pentazocine in tight, light-resistant containers.

CATEGORY—Analgesic.

USUAL DOSE—Parenteral, **30 mg.** (as the lactate) every 3 to 4 hours.

USUAL DOSE RANGE—**20** to **60 mg.**

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* Patented. See notice, page ii.

Pentazocine Lactate Injection*

Pentazocine Lactate Injection is a sterile solution of pentazocine lactate in water for injection, prepared from pentazocine with the aid of lactic acid. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{19}H_{27}NO$ (pentazocine).

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* Patented. See notice, page ii.

Identification—

A: The ultraviolet absorption spectrum of the *Assay preparation*, prepared as directed in the *Assay*, exhibits maxima and minima at the same wavelengths as that of the *Standard preparation*, prepared as directed in the *Assay*.

B: Evaporate to dryness a volume of Pentazocine Lactate Injection, equivalent to about 3 mg. of pentazocine: the residue responds to *Identification test A* under *Pentazocine*, page 528.

pH, page 824—The pH of Pentazocine Lactate Injection is between 4.0 and 5.0.

Other requirements—Pentazocine Lactate Injection meets the requirements under *Injections*, page 810.

Assay—

Ion-exchange column—Place a pledget of glass wool in the base of a 6-mm. (inside diameter) tube equipped with a stopcock, and fill the tube to a height of about 25 mm. with a styrene-divinylbenzene cation-exchange resin, page 911, which has been previously soaked in 3 *N* hydrochloric acid for at least 2 hours. Pass 10 ml. of methanol through the column followed by 50 ml. of 3 *N* hydrochloric acid, and then wash the column with water until the eluate is neutral. (*Caution:* Do not permit the column to become dry at any time.)

Standard preparation—Transfer about 60 mg. of NF Pentazocine Reference Standard, accurately weighed, to a 50-ml. volumetric flask, dilute to volume with a mixture of equal volumes of methanol and 6 *N* hydrochloric acid, and mix. Transfer 10.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with the methanol-6 *N* hydrochloric acid mixture, and mix.

Assay preparation—Dilute an accurately measured volume of Pentazocine Lactate Injection, equivalent to about 60 mg. of pentazocine base, to 10.0 ml. with water, and mix. Transfer 2.0 ml. of this solution to the column, then pass 100 ml. of water through the column at a rate of about 2 ml. per minute, and discard the eluate. Place a 100-ml. volumetric flask under the column, and pass through the column sufficient of a mixture of equal volumes of methanol and 6 *N* hydrochloric acid until approximately 95 ml. of eluate has been collected. Remove the flask, dilute to volume with the methanol-6 *N* hydrochloric acid mixture, and mix.

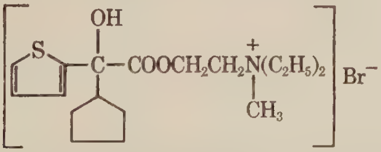
Procedure—Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 278 mμ, with a suitable spectrophotometer, using a mixture of equal volumes of methanol and 6 *N* hydrochloric acid as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{19}H_{27}NO$ (pentazocine base) in each ml. of the Injection by the formula $0.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration of the *Standard preparation*, in mcg. per ml., and V is the volume, in ml., of the Injection taken.

Packaging and storage—Preserve Pentazocine Lactate Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injection available—Pentazocine Lactate Injection usually available contains pentazocine lactate equivalent to the following amount of pentazocine base: 30 mg. in 1 ml.

Category and Dose—See Pentazocine.

Penthienate Bromide



Diethyl(2-hydroxyethyl)methylammonium Bromide α-Cyclopentyl-2-thiopheneglycolate

$C_{18}H_{30}BrNO_3S$ Mol. wt. 420.41

Penthienate Bromide, dried at 60° in vacuum to constant weight, contains not less than 98.0 percent and not more than 100.5 percent of $C_{18}H_{30}BrNO_3S$.

Description—Penthienate Bromide occurs as a white, odorless, crystalline powder.

Solubility—Penthienate Bromide is soluble in water and in alcohol. It is freely soluble in chloroform, and is practically insoluble in acetone and in ether.

Identification—A solution of Penthienate Bromide responds to the tests for *Bromide,* page 808.

Melting range, page 814—Penthienate Bromide melts between 122° and 128°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Penthienate Bromide, previously dried in vacuum at 60° to constant weight, exhibits maxima only at the same wavelengths as that of NF Penthienate Bromide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Penthienate Bromide in 0.02 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Penthienate Bromide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 238 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Penthienate Bromide at 60° in vacuum to constant weight: it loses not more than 1 percent of its weight.

Assay—Dissolve about 800 mg. of Penthienate Bromide, previously dried at 60° in vacuum to constant weight and accurately weighed, in 50 ml. of glacial acetic acid, add 15 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 42.04 mg. of $C_{18}H_{30}BrNO_3S$.

Packaging and storage—Preserve Penthienate Bromide in tight containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**5 mg.** three or four times a day.

USUAL DOSE RANGE—**2.5** to **10 mg.**

Penthienate Bromide Tablets

Penthienate Bromide Tablets contain not less than 92.0 percent and not more than 108.0 percent of the labeled amount of $C_{18}H_{30}BrNO_3S$.

Identification—

A: Evaporate on a steam bath to a small volume each of the remaining ether-chloroform solutions obtained from the *Standard preparation* and the *Assay preparation* in the *Assay.* Complete the evaporation without heat, dry in vacuum at 60°, and dissolve the α-cyclopentyl-2-thiopheneglycolic acid residue so obtained in 0.25 ml. of chloroform. The infrared absorption spectrum of the solution obtained from the *Assay preparation,* determined in a 0.5-mm. cell, exhibits maxima only at the same wavelengths as that of the solution obtained from the *Standard preparation,* similarly measured.

B: Shake a quantity of finely powdered Penthienate Bromide Tablets, equivalent to about 10 mg. of penthienate bromide, with 10 ml. of 0.1 *N* sulfuric acid, filter, and add 2 ml. of ammonium reineckate T.S.: a violet-pink precipitate is formed.

Disintegration, page 878—The disintegration time limit for Penthienate Bromide Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Penthienate Bromide Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Dissolve about 100 mg. of NF Penthienate Bromide, previously dried in vacuum at 60° to constant weight and accurately weighed, in sufficient water to make 250.0 ml., and mix.

Assay preparation—Weigh and finely powder not less than 40 Penthienate Bromide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg. of penthienate bromide, to a 250-ml. volumetric flask, add about 150 ml. of water, and shake mechanically for 15 minutes. Dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate.

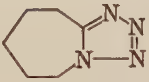
Procedure—Pipet 25.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate 125-ml. separators, and add 1 ml. of diluted hydrochloric acid. Extract each solution with 15 ml. of ether, and transfer the aqueous portion to a second separator. Wash the ether extract with two successive 2-ml. portions of water, adding the washings to the aqueous solution. Discard the ether extract. Add 10 ml. of sodium hydroxide T.S., mix, and allow to stand for 20 minutes. Acidify with 5 ml. of diluted hydrochloric acid and extract the solution with two successive 45-ml. portions of a mixture of ether-chloroform (1:1), filtering each portion through chloroform-washed paper into a 100-ml. volumetric flask. Dilute to volume with ether-chloroform (1:1), and mix. Transfer 5.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask, evaporate to dryness with a stream of air, dissolve the residue in 25.0 ml. of methanol, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 238 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{18}H_{30}BrNO_3S$ in the portion of the Tablets taken, by the formula $0.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Penthienate Bromide in the *Standard preparation*, and A_U and A_S are the absorbances of the solutions obtained from the *Assay preparation* and *Standard preparation*, respectively.

Packaging and storage—Preserve Penthienate Bromide Tablets in well-closed containers.

Tablets available—Penthienate Bromide Tablets usually available contain the following amount of penthienate bromide: 5 mg.

CATEGORY and DOSE—See Penthienate Bromide.

Pentylenetetrazol



6,7,8,9-Tetrahydro-5*H*-tetrazoloazepine

$C_6H_{10}N_4$ Mol. wt. 138.17

Pentylenetetrazol, previously dried over phosphorus pentoxide for 18 hours, contains not less than 99.0 percent and not more than 101.0 percent of $C_6H_{10}N_4$.

Description—Pentylenetetrazol occurs as white crystals. It is odorless and has a slightly pungent, bitter taste. Its 1 in 10 solution is neutral to litmus.

Solubility—Pentylenetetrazol is freely soluble in water and in alcohol. It is soluble in ether, in chloroform, and in carbon tetrachloride.

Identification—To a solution of Pentylenetetrazol (1 in 10) add a saturated solution of mercuric chloride: a white precipitate is formed.

Melting range, page 814—Pentylenetetrazol melts between 58° and 61°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Pentylenetetrazol, previously dried over phosphorus pentoxide for 18 hours, exhibits maxima only at the same wavelengths as that of NF Pentylenetetrazol Reference Standard, similarly measured.

Loss on drying, page 814—Dry Pentylenetetrazol over phosphorus pentoxide for 18 hours: it loses not more than 0.2 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 200 mg. of Pentylenetetrazol, using a platinum dish, is negligible.

Ether-insoluble substances—Digest 200 mg. of Pentylenetetrazol, accurately weighed, with 20 ml. of ether in a closed flask for 30 minutes with frequent agitation. If an undissolved residue remains, decant the liquid through a small, tared, filtering crucible, and digest the residue with 10 ml. of ether for 20 minutes with frequent agitation. Transfer the residue to the filtering crucible, wash the flask and crucible with five 3-ml. portions of ether, dry the crucible at 105° for 1 hour, cool, and weigh: the weight of the ether-insoluble residue does not exceed 2 mg. (1 percent).

Assay—Transfer about 1.0 g. of Pentylenetetrazol, previously dried over phosphorus pentoxide for 18 hours and accurately weighed, into a 100-ml. volumetric flask, dissolve in about 50 ml. of water, add water to volume, and mix. Transfer 10.0 ml. of this solution to a 150-ml. beaker containing 1.5 g. of phosphotungstic acid, 10 ml. of 0.1 *N* sulfuric acid, and 20 ml. of 0.1 *N* silver nitrate which have been added in the order mentioned. Heat the solution to boiling, boil for 5 minutes, and allow to stand in a refrigerator for 30 minutes. Collect the precipitate on a tared, fine-porosity, sintered-glass crucible, and wash thoroughly with small portions of cold water. Dry the crucible and contents at 105° for 4 hours, cool and weigh. The weight of the precipitate so obtained, multiplied by 0.1472, represents the weight of $C_6H_{10}N_4$ in the Pentylenetetrazol taken.

Packaging and storage—Preserve Pentylenetetrazol in tight containers.

CATEGORY—Central stimulant.

USUAL DOSE—Intravenous and subcutaneous. Initial, **500 mg.,** then adjust dosage and repeat at 30-minute intervals as needed.

USUAL DOSE RANGE—**100 mg.** to **2 g.**

Pentylenetetrazol Injection

Pentylenetetrazol Injection is a sterile solution of pentylenetetrazol in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{10}N_4$.

Identification—Pentylenetetrazol Injection responds to the *Identification test* under *Pentylenetetrazol,* page 531.

pH, page 824—The pH of Pentylenetetrazol Injection is between 6.0 and 8.5.

Other requirements—Pentylenetetrazol Injection meets the requirements under *Injections,* page 810.

Assay—

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25 × 200-mm. test tube to which is fused a 5-cm. length of 6 or 8-mm. tubing) with the aid of a tamping rod of stainless steel, aluminum, or glass, at least 30 cm. long and having a terminal disk with a diameter of about 1 mm. less than that of the chromatographic tube. To 2.0 g. of purified siliceous earth in a 100-ml. beaker, add 2.0 ml. of sodium hydroxide T.S., and incorporate by kneading thoroughly with a flexible spatula blade until the mixture is fluffy. Transfer to the chromatographic tube and tamp gently to compress the material to a uniform mass. In a like manner, mix intimately 2.0 g. of purified siliceous earth with 2.0 ml. of 1 *N* sulfuric acid, transfer to the column, and gently compress with the tamping rod.

Procedure—Transfer an accurately measured amount of Pentylenetetrazol Injection, equivalent to about 200 mg. of pentylenetetrazol, to a 100-ml. beaker containing 2.0 g. of purified siliceous earth. Mix as directed under *Chromatographic column,* and transfer to the prepared column. Dry wash the beaker with an additional portion of adsorbant, transfer it to the column, and gently compress with the tamping rod. Place a pledget of glass wool on the top of the column. Elute the column with 50 ml. of water-saturated chloroform collecting the eluate in a suitable vessel. Evaporate the eluate on a steam bath under a gentle stream of air to a volume of 3 ml., transfer the residue with the aid of chloroform to a 10-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Pentylenetetrazol Reference Standard, in the same medium, at a concentration of about 20 mg. per ml., in 1-mm. cells, at the maximum at about 10.05 μ and at the minimum at about 10.25 μ, with a suitable infrared spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_6H_{10}N_4$ in each ml. of the Injection taken by the formula $10 \times (C/V) \times (A_{U10\cdot05} - A_{U10\cdot25})/(A_{S10\cdot05} - A_{S10\cdot25})$, in which C is the exact concentration of the standard solution, in mg. per ml., V is the volume, in ml., of the Injection taken, and A_U and A_S are the absorbances of the sample solution and the Reference Standard solution, respectively, at the wavelengths indicated by the subscripts.

Packaging and storage—Preserve Pentylenetetrazol Injection in single-dose or in multiple-dose containers. It may be packaged in 100-ml. multiple-dose containers.

Injections available—Pentylenetetrazol Injection usually available contains the following amounts of pentylenetetrazol: 100 mg. in 1 ml.; 300 mg. in 3 ml.; 3 g. in 30 ml.; 10 g. in 100 ml.

CATEGORY and DOSE—See Pentylenetetrazol.

Peppermint Spirit

Peppermint Spirit contains, in each 100 ml., not less than 9.0 ml. and not more than 11.0 ml. of peppermint oil.

Peppermint Oil	**100 ml.**
Peppermint, in coarse powder	**10 g.**
Alcohol, a sufficient quantity,	
To make	**1000 ml.**

Macerate the peppermint leaves, freed as much as possible from stems and coarsely powdered, for 1 hour in 500 ml. of purified water, and then strongly express them. Add the moist, macerated leaves to 900 ml. of alcohol, and allow the mixture to stand for 6 hours with frequent agitation. Filter, and to the filtrate add the oil and sufficient alcohol to make the product measure 1000 ml.

Assay—Pipet 5.0 ml. of Peppermint Spirit into a Babcock bottle, graduated to 8 percent, add from a 1-ml. pipet 1.0 ml. of kerosene, and mix. Add sufficient saturated calcium chloride solution, acidified with hydrochloric acid, almost to fill the bulb of the bottle. Rotate the bottle vigorously to ensure mixing, then add a sufficient quantity of the calcium chloride solution to bring the separated oil into the neck of the bottle. Centrifuge for 5 minutes at about 1500 revolutions per minute, and read the volume of oil in the stem. Subtract 5 divisions for the kerosene added, and multiply the remaining number of divisions by 4.2 to obtain the volume, in ml., of peppermint oil in 100 ml. of the Spirit.

Alcohol content, page 772—Peppermint Spirit contains from 79 to 85 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Peppermint Spirit in tight containers, protected from light.

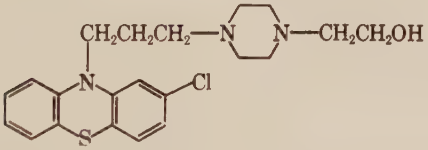
CATEGORY—Digestive aid; flavor.
USUAL DOSE—**1 ml.** three times a day.

Peppermint Water

Peppermint Water is a clear, saturated solution of peppermint oil in purified water, prepared by one of the processes described under *Aromatic Waters*, page 826.

CATEGORY—Vehicle.

Perphenazine*



4-[3-(2-Chlorophenothiazin-10-yl)propyl]-1-piperazineethanol

$C_{21}H_{26}ClN_3OS$ Mol. wt. 403.98

Perphenazine, dried at 65° in vacuum for 3 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{26}ClN_3OS$.

Description—Perphenazine occurs as a white to creamy white, odorless powder.

Solubility—Perphenazine is practically insoluble in water. It is freely soluble in alcohol and in chloroform, and is soluble in acetone.

Clarity and color of solution—Dissolve 500 mg. of Perphenazine in 25 ml. of methanol: the solution is clear and not more than light yellow.

Identification—Dissolve about 10 mg. of Perphenazine in 5 ml. of methanol, and add 10 ml. of sulfuric acid-methanol mixture (4:1): a pink color develops. Add 2 drops of ferric ammonium sulfate T.S.: a reddish purple color develops.

Melting range, page 814—Perphenazine melts between 94° and 100°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Perphenazine, previously dried at 65° in vacuum for 3 hours, exhibits maxima only at the same wavelengths as that of NF Perphenazine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Perphenazine in methanol exhibits maxima and minima at the same wavelengths as that of NF Perphenazine Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 257 mμ, do not differ by more than 2.5 percent.

Loss on drying, page 814—Dry Perphenazine at 65° in vacuum for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Perphenazine yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 400 mg. of Perphenazine, previously dried at 65° in vacuum for 3 hours and accurately weighed, in 50 ml. of glacial acetic acid, warming slightly to effect solution. Cool to room temperature, add 10 ml. of acetic anhydride, and allow to stand for 5 minutes. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Each ml. of 0.1 *N* perchloric acid is equivalent to 20.20 mg. of $C_{21}H_{26}ClN_3OS$.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Perphenazine in tight containers.

CATEGORY—Tranquilizer (major).

USUAL DOSE RANGE—Oral: nonhospitalized patients, **2** to **8 mg.** three times a day; hospitalized patients, **8** to **16 mg.** two to four times a day. Intramuscular, **5** to **10 mg.** initially, followed by **5 mg.** in 6 hours.

Perphenazine Injection

Perphenazine Injection is a sterile solution of perphenazine in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{26}ClN_3OS$.

Identification—

A: To 2 ml. of Perphenazine Injection add cautiously 2 ml. of sulfuric acid: a pink color develops. Add 1 drop of ferric ammonium sulfate T.S.: a reddish purple color develops.

B: The solution prepared for measurement of absorbance in the *Assay* exhibits maxima at about 254 mμ and 308 mμ, and a minimum at about 280 mμ.

pH, page 824—The pH of Perphenazine Injection is between 4.2 and 5.6.

Other requirements—Perphenazine Injection meets the requirements under *Injections*, page 810.

Assay—Pipet a volume of Perphenazine Injection, equivalent to about 50 mg. of perphenazine, into a 250-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Pipet 5.0 ml. of this solution into a 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Perphenazine Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 254 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{21}H_{26}ClN_3OS$ in each ml. of the Injection taken, by the formula $5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Injection taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Perphenazine Injection in single-dose or multiple-dose containers, preferably of Type I glass, protected from light.

Injections available—Perphenazine Injection usually available contains the following amounts of perphenazine: 5 mg. in 1 ml.; 50 mg. in 10 ml.

CATEGORY and DOSE—See Perphenazine.

Perphenazine Tablets

Perphenazine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{26}ClN_3OS$.

Identification—

A: Digest about 1 g. of finely powdered Perphenazine Tablets with 5 ml. of methanol, and filter. The filtrate responds to the *Identification test* under *Perphenazine*, page 533.

B: The solution prepared for measurement of absorbance in the *Assay* exhibits maxima at about 254 mμ and 308 mμ, and a minimum at about 280 mμ.

Disintegration, page 878—The disintegration time limit for Perphenazine Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Perphenazine Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Place one tablet in a 100-ml. volumetric flask, add 50 ml. of 0.1 *N* hydrochloric acid, and shake mechanically until the tablet is completely disintegrated. Dilute to volume with 0.1 *N* hydrochloric acid, filter, and quantitatively dilute a portion of the filtrate to provide a solution containing approximately 10 mcg. per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Perphenazine Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 254 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{21}H_{26}ClN_3OS$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which *T* is the labeled quantity, in mg., of perphenazine in the tablet; *D* is the exact concentration, in mcg. per ml., of the sample solution, based upon the labeled quantity per tablet and the extent of dilution; *C* is the exact concentration, in mcg. per ml., of Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Perphenazine Tablets. Weigh accurately a portion of the powder, equivalent to about 4 mg. of perphenazine, and transfer to a separator. Add ammonia T.S. until the pH is about 11, and extract with five 20-ml. portions of ether. Extract the combined ether extracts with four 20-ml. portions of 0.1 *N* hydrochloric acid, then dilute the combined acid extracts to 100.0 ml. with 0.1 *N* hydrochloric acid, and mix. Dilute 20.0 ml. of this solution to 100.0 ml. with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Perphenazine Reference Standard in the same medium at a concentration of about 8 mcg. per ml., in 1-cm. cells, at the maximum at about 254 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{21}H_{26}ClN_3OS$ in the portion of the Tablets taken by the formula $0.5C \times (A_U/A_S)$, in which *C* is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard Solution.

Packaging and storage—Preserve Perphenazine Tablets in tight containers.

Tablets available—Perphenazine Tablets usually available contain the following amounts of perphenazine: 2, 4, 8, and 16 mg.

CATEGORY and DOSE—See Perphenazine.

Persic Oil

Persic Oil is the oil expressed from the kernels of varieties of *Prunus armeniaca* Linné (Apricot Kernel Oil), or from the kernels of varieties of *Prunus persica* Sieb. et Zucc. (Peach Kernel Oil) (Fam. *Rosaceæ*).

Description—Persic Oil is a clear, pale straw-colored or colorless, oily liquid. It is almost odorless, and has a bland taste. It is not turbid at temperatures above 15°.

Solubility—Persic Oil is slightly soluble in alcohol. It is miscible with ether, with chloroform, with benzene, and with solvent hexane.

Specific gravity, page 866—The specific gravity of Persic Oil is not less than 0.910 and not more than 0.923.

Mineral oil—Heat on a steam bath 10 ml. of Persic Oil with 15 ml. of sodium hydroxide solution (1 in 6) and 30 ml. of alcohol in a flask having a small, short-stemmed funnel inserted in the neck, and occasionally agitate the mixture until it becomes clear. Transfer the solution to a shallow dish, evaporate the alcohol on a steam bath, and mix the residue with 100 ml. of water: a clear solution results.

Cottonseed oil—Mix 5 ml. of Persic Oil in a test tube with 5 ml. of a mixture of equal volumes of amyl alcohol and of a 1 percent solution of sulfur in carbon disulfide, warm the mixture carefully until the carbon disulfide is expelled, and immerse the test tube to one-third of its length in a boiling, saturated solution of sodium chloride: the mixture develops no reddish color within 2 hours.

Sesame oil—Mix 10 ml. of Persic Oil with 10 ml. of hydrochloric acid, add 0.1 ml. of an alcohol solution of furfural (1 in 50), and shake the mixture vigorously for 15 seconds: no pink to crimson color appears in the acid layer when separate layers form. Should any color appear in the acid layer, add 10 ml. of water, and again shake the mixture vigorously. In the absence of sesame oil the pink color is fugitive.

Free fatty acids, page 804—The free fatty acids in 10 g. of Persic Oil require for neutralization not more than 2 ml. of 0.02 *N* sodium hydroxide.

Iodine value, page 804—The iodine value of Persic Oil is not less than 90 and not more than 108.

Saponification value, page 805—The saponification value of Persic Oil is not less than 185 and not more than 195.

Packaging and storage—Preserve Persic Oil in tight containers.

Labeling—Label Persic Oil to indicate whether it was derived from apricot kernels or from peach kernels.

CATEGORY—Vehicle.

Peruvian Balsam

Peruvian Balsam is obtained from *Myroxylon pereiræ* (Royle) Klotzsch (Fam. *Leguminosæ*).

Description—Peruvian Balsam is a dark brown, viscid liquid. It is transparent and appears reddish brown in thin layers. It has an agreeable odor resembling vanilla, a bitter, acrid taste, with a persistent after-taste, and is free from stringiness or stickiness. It does not harden on exposure to air.

Solubility—Peruvian Balsam is nearly insoluble in water, but is soluble in alcohol, in chloroform, and in glacial acetic acid, with not more than an opalescence. It is only partly soluble in ether and in solvent hexane.

Specific gravity, page 866—The specific gravity of Peruvian Balsam is not less than 1.150 and not more than 1.170.

Fixed oils—Shake one g. of Peruvian Balsam with a solution of 3 g. of chloral hydrate in 2 ml. of water: a clear solution forms.

Rosin—Peruvian Balsam meets the requirements of the test for *Rosin*, page 859.

Turpentine—Shake about 1 g. of Peruvian Balsam with 5 ml. of solvent hexane and warm the mixture on a steam bath for 10 minutes, adding a sufficient quantity of the solvent to replace that lost by evaporation. Evaporate 2 ml. of the filtered hexane solution: no odor of turpentine oil is perceptible.

Acid value, page 804—Dissolve about 1 g. of Peruvian Balsam, accurately weighed, in 100 ml. of neutralized alcohol, add 1 ml. of phenolphthalein T.S., and titrate with 0.5 *N* sodium hydroxide: the acid value is not less than 56 and not more than 84.

Cinnamein—Mix about 3 g. of Peruvian Balsam, accurately weighed, with 30 ml. of sodium hydroxide T.S. in a separator, shake the mixture for a few minutes with 100 ml. of ether, and allow it to stand until complete separation into two layers has taken place. Draw off the lower, water layer and quickly filter the ether layer into a 100-ml. volumetric flask, add ether to volume, and mix. Transfer 50 ml. of the ether solution (representing half of the weight of the Balsam taken) to a tared conical flask, evaporate the ether, and dry the residue at 100° for 30 minutes: the weight of the residue of cinnamein so obtained is equivalent to not less than 50 percent and not more than 60 percent of the weight of the Balsam represented by the 50 ml. of ether solution taken. Retain the residue.

Saponification value, page 805—Dissolve the residue obtained in the test for *Cinnamein* in 25 ml. of alcohol, add 25.0 ml. of 0.5 *N* alcoholic potassium hydroxide, and heat the mixture carefully on a steam bath for 30 minutes in a flask provided with a reflux condenser. Then add 1 ml. of phenolphthalein T.S., and titrate the excess alkali with 0.5 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations*, page 883). The total volume of 0.5 *N* alcoholic potassium hydroxide consumed is equivalent to a saponification value for the cinnamein of not less than 230 and not more than 240.

Packaging and storage—Preserve Peruvian Balsam in tight containers, and avoid exposure to excessive heat.

CATEGORY—Local protectant; rubefacient.

FOR EXTERNAL USE—Topically to skin as required, usually in ointment or in alcohol solution.

Petrolatum

Petrolatum is a purified mixture of semisolid hydrocarbons obtained from petroleum. It may contain a suitable stabilizer.

Description—Petrolatum is an unctuous mass, varying in color from yellowish to light amber. It has not more than a slight fluorescence even after being melted, and is transparent in thin layers. It is free or nearly free from odor and taste.

Solubility—Petrolatum is insoluble in water. It is almost insoluble in cold or hot alcohol, and in cold dehydrated alcohol. It is freely soluble in benzene, in carbon disulfide, in chloroform, and in turpentine oil. It is soluble in ether, in solvent hexane, and in most fixed and volatile oils.

Specific gravity, page 866—The specific gravity of Petrolatum is not less than 0.815 and not more than 0.880 at 60°.

Melting range, *Class III*, page 815—Petrolatum melts between 38° and 60°.

Consistency—

Apparatus—Determine the consistency of Petrolatum by means of a penetrometer fitted with a polished cone-shaped metal plunger weighing 150 g., having a detachable steel tip of the following dimensions: the tip of the cone has an angle of 30°, the point being truncated to a diameter of 0.38 ± 0.03 mm., and the base of the tip is 8.38 ± 0.05 mm. in diameter, and the length of the tip is 15 ± 0.25 mm. The remaining portion of the cone has an angle of 90°, is 28.2 mm. in height, and has a maximum diameter at the base of 65.1 mm. The containers for the test are flat-bottomed, metal or glass cylinders that are 102 ± 6 mm. in diameter and not less than 60 mm. in height.

Procedure—Melt a quantity of Petrolatum at 82 ± 2.5°, pour it into one or more of the containers, filling to within 6 mm. of the rim. Cool at 25 ± 2.5° over a period of not less than 16 hours, protected from drafts. Two hours before the test, place the containers in a water bath at 25 ± 0.5°. If the room temperature is below 23.5° or above 26.5°, adjust the temperature of the cone to 25 ± 0.5° by placing it in the water bath.

Without disturbing the surface of the sample, place the container on the penetrometer table, and lower the cone until the tip just touches the top surface of the sample at a spot 25 to 38 mm. from the edge of the container. Adjust the zero setting and quickly release the plunger, and hold it free for 5 seconds. Secure the plunger, and read the total penetration from the scale. Make 3 or more trials, each so spaced that there is no overlapping of the areas of penetration. Where the penetration exceeds 20 mm., use a separate container of the sample for each trial. Read the penetration to the nearest 0.1 mm. Calculate the average of the 3 or more readings and conduct further trials to a total of 10 if the individual results differ from the average by more than ±3 percent: the final average of the trials is not less than 10.0 mm. and not more than 30.0 mm. indicating a consistency value between 100 and 300.

Reaction—Introduce 35 g. of Petrolatum into a 250-ml. separator, add 100 ml. of boiling water, and shake vigorously for 5 minutes. After the Petrolatum and water have separated, draw off the water into a casserole, wash the Petrolatum in the separator with two 50-ml. portions of boiling water, and add the washings to the casserole. To the accumulated 200 ml. of water add 1 drop of phenolphthalein T.S., and boil: the solution does not acquire a pink color. If the addition of phenolphthalein produces no pink color, add 0.1 ml. of methyl orange T.S.: no red or pink color is produced.

Residue on ignition—Heat 2 g. of Petrolatum in an open porcelain or platinum dish over a Bunsen flame: it volatilizes without emitting an acrid odor, and on ignition yields not more than 0.05 percent of residue.

Organic acids—Weigh 20 g. of Petrolatum, add 100 ml. of a mixture of neutralized alcohol and water (1 in 2), agitate thoroughly, and heat to boiling. Add 1 ml. of phenolphthalein T.S., and titrate rapidly with 0.1 *N* sodium hydroxide, with vigorous agitation to the production of a sharp pink end-point, noting the color change in the alcohol-water layer: not more than 0.4 ml. of 0.1 *N* sodium hydroxide is required.

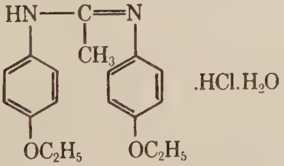
Fixed oils, fats, and rosin—Digest 10 g. of Petrolatum at 100° with 10 g. of sodium hydroxide and 50 ml. of water for 30 minutes. Separate the water layer, and add to it an excess of diluted sulfuric acid: no oily or solid matter separates.

Color—Melt about 10 g. of Petrolatum on a steam bath, and pour about 5 ml. of the liquid into a clear-glass bacteriological test tube, 150 × 15 mm., keeping the Petrolatum melted. The Petrolatum is not darker than a solution made by mixing 3.8 ml. of ferric chloride C.S. and 1.2 ml. of cobaltous chloride C.S. in a similar tube, the comparison of the two being made in reflected light against a white background, holding the Petrolatum tube directly against the background at such an angle that there is no fluorescence.

Packaging and storage—Preserve Petrolatum in tight containers.

CATEGORY—Ointment base.

Phenacaine Hydrochloride



N,*N′*-Bis(*p*-ethoxyphenyl)acetamidine Monohydrochloride

$C_{18}H_{22}N_2O_2 . HCl . H_2O$ Mol. wt. 352.86

Phenacaine Hydrochloride, dried at 105° for 6 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{22}N_2O_2 . HCl$.

Description—Phenacaine Hydrochloride occurs as small, white crystals. It is odorless, has a faintly bitter taste, producing transient numbness of the tongue, and is stable in air.

Solubility—Phenacaine Hydrochloride is sparingly soluble in water. It is freely soluble in alcohol and in chloroform, and is practically insoluble in ether.

Identification—

A: To 5 ml. of a saturated solution of Phenacaine Hydrochloride add a few drops of sodium hypochlorite T.S.: a flesh-colored precipitate is formed which changes in a few minutes to a violet color. When the mixture is shaken with ether, the ether becomes deep red.

B: A solution of Phenacaine Hydrochloride (1 in 100) responds to the tests for *Chloride*, page 808.

C: The phenacaine obtained in the *Assay*, recrystallized from hot alcohol and dried at 105° for 1 hour, melts between 116° and 118°, page 814.

Melting temperature, page 814—When dried at 105° for 6 hours, Phenacaine Hydrochloride melts at a temperature not below 190°.

Acidity—Dissolve 1 g. of Phenacaine Hydrochloride in 50 ml. of warm water, cool, and add 1 drop of methyl red T.S.: if a red color is produced, it requires not more than 0.5 ml. of 0.02 *N* sodium hydroxide to change it to yellow.

Loss on drying, page 814—Dry Phenacaine Hydrochloride at 105° for 6 hours: it loses not less than 4 percent and not more than 7 percent of its weight.

Residue on ignition, page 858—Phenacaine Hydrochloride yields not more than 0.15 percent of residue on ignition.

Phenacetin—Dissolve 50 mg. of Phenacaine Hydrochloride in 2 ml. of hydrochloric acid, boil for 2 minutes, cool, and add 1 drop of potassium dichromate T.S.: no ruby-red color is produced.

Assay—To about 25 ml. of water and 5 ml. of ammonia T.S. contained in a separator, add about 500 mg. of Phenacaine Hydrochloride, previously dried at 105° for 6 hours and accurately weighed. Extract this solution with four successive portions of 15, 10, 10, and 10 ml. of chloroform. Pass the chloroform extracts through chloroform-washed cotton in a small funnel into a tared beaker, and wash the cotton and funnel with a few ml. of chloroform. Cautiously evaporate the chloroform, adding 5 ml. of alcohol just before the last of the chloroform is expelled. Evaporate the alcohol, dry the residue at 105° for 1 hour, and weigh. The weight of the phenacaine so obtained, multiplied by 1.122, represents the weight of $C_{18}H_{22}N_2O_2.HCl$ in the Phenacaine Hydrochloride taken.

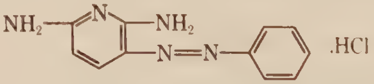
Packaging and storage—Preserve Phenacaine Hydrochloride in well-closed containers.

Category—Local anesthetic (ophthalmic).

Application—To the conjunctiva as a 1 percent solution or as a 1 to 2 percent ointment.

Phenacetin, Aspirin and Caffeine Tablets, page 66
Phenacetin, Aspirin, Caffeine and Codeine Phosphate Tablets, page 178

Phenazopyridine Hydrochloride



2,6-Diamino-3-(phenylazo)pyridine Monohydrochloride

$C_{11}H_{11}N_5.HCl$ Mol. wt. 249.70

Phenazopyridine Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $C_{11}H_{11}N_5.HCl$, calculated on the dried basis.

Description—Phenazopyridine Hydrochloride occurs as a light or dark red to dark violet, crystalline powder. It is odorless or has a slight odor. It melts at about 235° with decomposition.

Solubility—Phenazopyridine Hydrochloride is slightly soluble in water, in alcohol, and in chloroform.

Identification—

A: To 5 ml. of a solution of Phenazopyridine Hydrochloride (1 in 100) add 3 ml. of hydrochloric acid: the solution becomes deep orange-red. Add about 100 mg. of granulated zinc and warm gently: the solution becomes colorless.

B: To 5 ml. of a solution of Phenazopyridine Hydrochloride (1 in 100) add 3 ml. of trinitrophenol T.S.: a yellow precipitate is formed.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Phenazopyridine Hydrochloride, previously dried in vacuum over phosphorus pentoxide at 80° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Phenazopyridine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Phenazopyridine Hydrochloride in 0.1 *N* alcoholic sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Phenazopyridine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 390 $m\mu$, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Phenazopyridine Hydrochloride in vacuum over phosphorus pentoxide at 80° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Phenazopyridine Hydrochloride yields not more than 0.2 percent of residue on ignition.

Water-insoluble substances—Dissolve about 2 g. of Phenazopyridine Hydrochloride, accurately weighed, in 200 ml. of water, heat to boiling, and then heat on a steam bath in a covered container for 1 hour. Filter through a tared, fine-porosity sintered-glass crucible, wash thoroughly with water, and dry to constant weight at 105°: the weight of the residue does not exceed 2 mg. (0.1 percent).

Heavy metals, *Method II*, page 806—The heavy metals limit for Phenazopyridine Hydrochloride is 20 parts per million.

Assay—Transfer about 20 mg. of Phenazopyridine Hydrochloride, accurately weighed, to a 75-ml. coulometric cell, dissolve in 20 ml. of water and acetone (4:1), and add 1.0 ml. of diluted hydrochloric acid and a sufficient quantity of triple-distilled mercury to provide a suitable pool electrode. Immerse a saturated calomel reference electrode and a working platinum electrode into the sample solution, using appropriate salt bridges, and deaerate by bubbling nitrogen through the solution for approximately 10 minutes. Using a suitable controlled-potential coulometric titrator (see page 800), reduce the sample at −0.40 volt, with continued deaeration, until the observed cell current drops to $^1/_{1000}$ of the initial current. Perform a blank determination, and make any necessary correction. Each coulomb of electricity is equivalent to 646.9 mcg. of $C_{11}H_{11}N_5.HCl$.

Packaging and storage—Preserve Phenazopyridine Hydrochloride in tight containers.

CATEGORY—Analgesic (urinary tract).

USUAL DOSE—**100 mg.** three or four times a day.

Phenazopyridine Hydrochloride Tablets

Phenazopyridine Hydrochloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{11}H_{11}N_5.HCl$.

Identification—Extract a portion of finely powdered Phenazopyridine Hydrochloride Tablets, equivalent to about 100 mg. of phenazopyridine hydrochloride, with 10 ml. of water, and filter: the filtrate responds to the *Identification tests* under *Phenazopyridine Hydrochloride*, page 538.

Disintegration, page 878—The disintegration time limit for Phenazopyridine Hydrochloride Tablets is 20 minutes.

Weight variation, page 901—Phenazopyridine Hydrochloride Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 10 Phenazopyridine Hydrochloride Tablets. Weigh accurately a portion of the powder, equivalent to about 5 mg. of phenazopyridine hydrochloride, and transfer to a glass-stoppered centrifuge tube. Add 25.0 ml. of a mixture of water and acetone (4:1), shake to dissolve completely, and then centrifuge. Transfer 15.0 ml. of the supernatant liquid to a 75-ml. coulometric cell, and add 1.0 ml. of diluted hydrochloric acid and a sufficient quantity of triple-distilled mercury to provide a suitable pool electrode. Immerse a saturated calomel reference electrode and a working platinum electrode into the sample solution, using appropriate salt bridges, and deaerate by bubbling nitrogen through the solution for approximately 10 minutes. Using a suitable controlled-potential coulometric titrator (see page 800) reduce the sample at −0.40 volt, with continued deaeration, until the observed cell current drops to $^1/_{1000}$ of the initial current. Perform a blank determination, and make any necessary correction. Each coulomb of electricity is equivalent to 646.9 mcg. of $C_{11}H_{11}N_5.HCl$.

Packaging and storage—Preserve

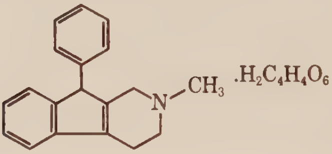
Phenazopyridine Hydrochloride Tablets in tight containers.

Tablets available—Phenazopyridine Hydrochloride Tablets usually available contain the following amounts of phenazopyridine hydrochloride: 100 and 200 mg.

CATEGORY and DOSE—See Phenazopyridine Hydrochloride.

Phenazopyridine Hydrochloride and Sulfisoxazole Tablets, page 679
Phenethicillin, Potassium, page 575
Phenethicillin, Potassium, for Oral Solution, page 576
Phenethicillin, Potassium, Tablets, page 576

Phenindamine Tartrate



2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine Tartrate (1:1)

$C_{19}H_{19}N\,.\,C_4H_6O_6$ Mol. wt. 411.46

Phenindamine Tartrate contains not less than 98.0 percent and not more than 101.5 percent of $C_{19}H_{19}N\,.\,C_4H_6O_6$, calculated on the dried basis.

Description—Phenindamine Tartrate occurs as a creamy white powder, usually having a very faint odor. Its solutions are acid to litmus.

Solubility—Phenindamine Tartrate is sparingly soluble in water, and is slightly soluble in alcohol. Phenindamine Tartrate is practically insoluble in chloroform, in ether, and in benzene.

Identification—

A: Dissolve 25 mg. of Phenindamine Tartrate in 5 ml. of sulfuric acid: the solution has an orange-brown color which disappears, leaving a clear solution when the mixture is diluted with 20 ml. of water.

B: Dissolve about 500 mg. of Phenindamine Tartrate in 15 ml. of hot water, add a slight excess of sodium hydroxide T.S. to liberate phenindamine, and filter: the clear filtrate, neutralized to litmus paper with diluted hydrochloric acid, responds to the tests for *Tartrate,* page 810.

C: Phenindamine Tartrate meets the requirements under *Identification—Organic Nitrogenous Bases,* page 810.

Melting range, *Class I,* page 815—Phenindamine Tartrate melts between 160° and 162°. When heated to about 163° it resolidifies, and at about 168° it melts again, with decomposition.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 40,000 solution of Phenindamine Tartrate in 0.5 *N* sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Phenindamine Tartrate Reference Standard, similarly measured, and the respective absorptivities calculated on the dried basis, at the point of maximum absorbance, occurring at about 260 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Phenindamine Tartrate at 105° for 3 hours: it loses not more than 1.5 percent of its weight.

Residue on ignition, page 858—Phenindamine Tartrate yields not more than 0.25 percent of residue on ignition.

Assay—Dissolve about 800 mg. of Phenindamine Tartrate, accurately weighed, in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 41.15 mg. of $C_{19}H_{19}N\,.\,C_4H_6O_6$.

Packaging and storage—Preserve Phenindamine Tartrate in tight, light-resistant containers.

CATEGORY—Antihistaminic.

USUAL DOSE—**25 mg.** up to four times a day as necessary.

USUAL DOSE RANGE—**25** to **50 mg.**

Phenindamine Tartrate Tablets

Phenindamine Tartrate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{19}H_{19}N . C_4H_6O_6$.

Identification—

A: To a portion of finely powdered Phenindamine Tartrate Tablets, equivalent to about 50 mg. of phenindamine tartrate, add 5 ml. of water and 3 ml. of ammonia T.S., and extract the liberated base with two successive 10-ml. portions of ether. Wash the combined ether extracts with 2 ml. of water, and evaporate to dryness: the residue so obtained responds to *Identification test A* under *Phenindamine Tartrate*, page 540.

B: Phenindamine Tartrate Tablets meet the requirements under *Identification—Organic Nitrogenous Bases*, page 810.

Disintegration, page 878—The disintegration time limit for Phenindamine Tartrate Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Phenindamine Tartrate Tablets meet the requirements of the content uniformity test for tablets.

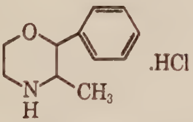
Assay—Proceed with Phenindamine Tartrate Tablets as directed under *Salts of Organic Nitrogenous Bases*, page 865, determining the absorbance at the maximum at about 260 mμ. Calculate the quantity, in mg., of $C_{19}H_{19}N . C_4H_6O_6$ in the portion of the Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the concentration, in mcg. per ml., calculated on the dried basis, of NF Phenindamine Tartrate Reference Standard in the *Standard preparation*.

Packaging and storage—Preserve Phenindamine Tartrate Tablets in tight, light-resistant containers.

Tablets available—Phenindamine Tartrate Tablets usually available contain the following amount of phenindamine tartrate: 25 mg.

CATEGORY and DOSE—See Phenindamine Tartrate.

Phenmetrazine Hydrochloride*



3-Methyl-2-phenylmorpholine Hydrochloride

$C_{11}H_{15}NO . HCl$ Mol. wt. 213.71

Phenmetrazine Hydrochloride, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{11}H_{15}NO . HCl$.

Description—Phenmetrazine Hydrochloride occurs as a white to off-white, crystalline powder.

Solubility—Phenmetrazine Hydrochloride is very soluble in water and is freely soluble in alcohol and in chloroform.

Melting range, *Class Ia*, page 815—Phenmetrazine Hydrochloride melts within a range of 3° between 172° and 182°.

Infrared absorption, page 866—The infrared absorption spectrum of Phenmetrazine Hydrochloride, previously dried at 105° for 2 hours, in chloroform (1 in 20), determined in a 0.1-mm. cell, exhibits maxima only at the same wavelengths as that of NF Phenmetrazine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2000 solution of Phenmetrazine Hydrochloride in dilute hydrochloric acid (4 in 100) exhibits maxima and minima at the same wavelengths as that of NF Phenmetrazine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 256 mμ, do not differ by more than 2 percent.

Loss on drying, page 814—Dry Phenmetrazine Hydrochloride at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Phenmetrazine Hydrochloride yields not more than 0.1 percent of residue on ignition. Retain the residue for the *Heavy metals test*.

Heavy metals, page 806—Dissolve the residue obtained under *Residue on ignition* in 2 ml. of hydrochloric acid, and complete the preparation of the sample solution as directed under *Method II*, page 806: the heavy metals limit for Phenmetrazine Hydrochloride is 10 parts per million.

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* Patented. See notice, page ii.

Sulfate, page 784—A 2-g. portion of Phenmetrazine Hydrochloride shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (0.01 percent).

pH, page 824—The pH of a solution (1 in 40) of Phenmetrazine Hydrochloride is between 4.5 and 5.5.

Assay—Transfer about 350 mg. of Phenmetrazine Hydrochloride, previously dried at 105° for 2 hours and accurately weighed, to a 250-ml. beaker. Add about 125 ml. of water and 10 drops of sulfuric acid, and stir for 15 minutes with a magnetic stirrer. Titrate the solution potentiometrically with 0.1 *N* silver nitrate, using silver chloride and calomel electrodes. (The calomel electrode contains saturated potassium sulfate solution.) Each ml. of 0.1 *N* silver nitrate is equivalent to 21.37 mg. of $C_{11}H_{15}NO.HCl$.

Packaging and storage—Preserve Phenmetrazine Hydrochloride in tight containers.

CATEGORY—Anorexic.

USUAL DOSE RANGE—**25** to **75 mg.** per day, in divided doses, administered 1 hour before meals.

Phenmetrazine Hydrochloride Tablets

Phenmetrazine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{11}H_{15}NO.HCl$.

Identification—Dissolve 5 Phenmetrazine Hydrochloride Tablets in 40 ml. of water and transfer the solution to a 250-ml. separator. Add 3 ml. of sodium hydroxide solution (1 in 2), and extract with two 50-ml. portions of chloroform. Extract the combined chloroform extracts in a 250-ml. separator with two 15-ml. portions of hydrochloric acid solution (4 in 100), and evaporate the combined aqueous extracts to dryness on a steam bath. Dissolve the residue in 5 ml. of acetone, and add 50 ml. of anhydrous ether to the solution. On standing phenmetrazine hydrochloride will crystallize out. Filter the precipitate, wash with anhydrous ether, and dry at 105°: the crystals so obtained melt within a range of 3° between 172° and 182°, page 814.

Disintegration, page 878—The disintegration time limit for Phenmetrazine Hydrochloride Tablets, determined in simulated gastric fluid T.S. without the use of disks, is 12 minutes.

Content uniformity, *Method I*, page 799—Phenmetrazine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Phenmetrazine Hydrochloride Tablets. Transfer to a 250-ml. volumetric flask an accurately weighed portion of the powder, equivalent to about 250 mg. of phenmetrazine hydrochloride, add about 125 ml. of dilute hydrochloric acid (4 in 100), shake mechanically for 1 hour, dilute to volume with hydrochloric acid solution (4 in 100), and mix. Pipet 50.0 ml. of the solution into a 250-ml. separator, add 5 ml. of sodium hydroxide solution (1 in 2), and extract with four 50-ml. portions of chloroform, collecting the chloroform extracts in a second 250-ml. separator. Extract the combined chloroform extracts with six 15-ml. portions of dilute hydrochloric acid (4 in 100), collecting the aqueous extracts in a 100-ml. volumetric flask, and dilute to volume with dilute hydrochloric acid (4 in 100). Concomitantly determine the absorbance of this solution and of a solution of NF Phenmetrazine Hydrochloride Reference Standard, in the same medium at a concentration of about 500 mcg. per ml., in 1-cm. cells, at the maximum at about 256 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (4 in 100) as the blank. Calculate the quantity, in mg., of $C_{11}H_{15}NO.HCl$ in the portion of the Tablets taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

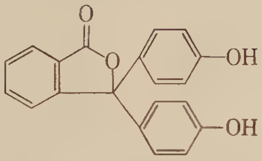
Packaging and storage—Preserve Phenmetrazine Hydrochloride Tablets in tight containers.

Tablets available—Phenmetrazine Hydrochloride Tablets usually available contain the following amount of phenmetrazine hydrochloride: 25 mg.

CATEGORY and DOSE—See Phenmetrazine Hydrochloride.

Phenobarbital, Ephedrine Hydrochloride and Theophylline Tablets, page 695
Phenobarbital and Ephedrine Sulfate Capsules, page 266

Phenolphthalein



3,3-Bis(*p*-hydroxyphenyl)phthalide

$C_{20}H_{14}O_4$ Mol. wt. 318.33

Phenolphthalein contains not less than 97.0 percent and not more than 101.0 percent of $C_{20}H_{14}O_4$, calculated on the dried basis.

Description—Phenolphthalein occurs as a white or faintly yellowish white, crystalline powder. It is odorless, and is stable to air.

Solubility—Phenolphthalein is practically insoluble in water. It is soluble in alcohol, and is sparingly soluble in ether.

Identification—Phenolphthalein is readily dissolved by solutions of alkali hydroxides and by hot solutions of alkali carbonates, yielding red liquids. These solutions are decolorized by the addition of an excess of acid or by high concentrations of alkali hydroxides.

Melting temperature, page 814—The melting temperature of Phenolphthalein is not lower than 258°.

Loss on drying, page 814—Dry Phenolphthalein over phosphorus pentoxide for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Phenolphthalein yields not more than 0.1 percent of residue on ignition.

Arsenic—A *Test Preparation* prepared with 1.25 g. of Phenolphthalein, as directed for organic compounds, meets the requirements of the *Arsenic Test,* page 777 (8 parts per million As).

Heavy metals, page 806—Heat 500 mg. of Phenolphthalein with 10 ml. of diluted acetic acid on a steam bath for 5 minutes, filter, and evaporate the filtrate to dryness. To the residue add 1 ml. of 0.1 *N* acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Phenolphthalein is 15 parts per million.

Color of solution—A solution of 500 mg. of Phenolphthalein in 30 ml. of alcohol has no more color than Matching Fluid A (see page 856).

Fluoran—A 500-mg. portion of Phenolphthalein dissolves completely in a mixture of 4 ml. of sodium hydroxide T.S. and 50 ml. of water.

Assay—Transfer about 100 mg. of Phenolphthalein, accurately weighed, to a 250-ml. iodine flask, add 5 ml. of dimethylformamide and agitate carefully until the sample has dissolved completely. Add 25 ml. of 0.2 *M* sodium carbonate, 25 ml. of 0.2 *M* sodium bicarbonate, and 50.0 ml. of 0.1 *N* iodine, and swirl the mixture gently for about 1 minute. Add 10 ml. of chloroform, 5 ml. of 4 *N* sulfuric acid, and titrate the excess iodine with 0.1 *N* sodium thiosulfate, adding 3 drops of starch T.S. as the end-point is neared. Each ml. of 0.1 *N* iodine is equivalent to 3.979 mg. of $C_{20}H_{14}O_4$.

Packaging and storage—Preserve Phenolphthalein in well-closed containers.

CATEGORY—Cathartic.
USUAL DOSE—**60 mg.**

Phenolphthalein Tablets

Phenolphthalein Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $C_{20}H_{14}O_4$.

Identification—Phenolphthalein Tablets produce a red liquid when mixed with alkali hydroxide solutions or with hot alkali carbonate solutions. The red liquid is decolorized by the addition of an excess of acid.

Disintegration, page 878—The disintegration time limit for Phenolphthalein Tablets is 30 minutes.

Weight variation, page 901—Phenolphthalein Tablets meet the requirements of the weight variation test for tablets.

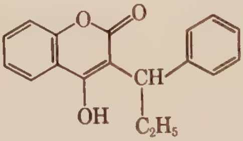
Assay—Weigh and finely powder not less than 20 Phenolphthalein Tablets. Transfer to a conical flask, an accurately weighed portion of the powder, equivalent to about 650 mg. of phenolphthalein, add 60 ml. of alcohol and boil the mixture gently for 20 minutes, rotating the flask occasionally. Cool the mixture, transfer it quantitatively to a 100-ml. volumetric flask, add alcohol to the mark, and mix thoroughly. Filter the mixture, covering the funnel with a watch glass, transfer to a beaker 20.0 ml. of the filtrate, equivalent to about 130 mg. of phenolphthalein, and evaporate it to dryness on a steam bath. Add 4 drops, or more if necessary, of a solution of potassium hydroxide (1 in 1), dilute the mixture with 5 ml. of water, and agitate carefully until the phenolphthalein has dissolved completely. Place the beaker in an ice and salt bath, and keep the solution at a temperature of from 0° to 5°. Add about 4.5 ml. of an iodine solution (dissolve 7 g. of iodine in 10 ml. of a saturated potassium iodide solution, dilute to 60 ml. with water, and add sufficient of the potassium hydroxide solution to discharge the iodine color), then add hydrochloric acid, dropwise, with constant stirring, until precipitation is complete. At this point the supernatant liquid must be deep brown in color, for a pale yellow color indicates that insufficient iodine solution has been used. Finally, add sufficient of the potassium hydroxide solution, dropwise, to dissolve the precipitate completely, though a little material may remain undissolved if fat is present. Repeat the process of precipitation and re-solution with hydrochloric acid and the potassium hydroxide solution several times, keeping the solution cold. Add 1 to 2 ml. of sodium sulfite solution (1.5 in 10) and, if necessary to remove fat, filter the mixture through a filter crucible, washing several times with cold water. Acidify the solution with hydrochloric acid, add a few ml. in excess, and heat the mixture on a steam bath for 30 minutes. Filter the mixture through a tared filter crucible, and wash the precipitate several times with cold water and finally with a small amount of solvent hexane. Dry the crucible and its contents at 130° for 3 hours, cool, and weigh. The weight of the precipitate, multiplied by 0.3873, represents the weight of $C_{20}H_{14}O_4$ in the portion of the filtrate taken.

Packaging and storage—Preserve Phenolphthalein Tablets in tight containers.

Tablets available—Phenolphthalein Tablets usually available contain the following amounts of phenolphthalein: 60 and 120 mg.

CATEGORY and DOSE—See Phenolphthalein.

Phenprocoumon*



3-(α-Ethylbenzyl)-4-hydroxycoumarin

$C_{18}H_{16}O_3$ Mol. wt. 280.33

Phenprocoumon contains not less than 99.0 percent and not more than 101.0 percent of $C_{18}H_{16}O_3$, calculated on the dried basis.

Description—Phenprocoumon occurs as a fine, white crystalline powder. It is odorless or has a slight odor.

Solubility—Phenprocoumon is practically insoluble in water. It is soluble in chloroform, in methanol, and in solutions of alkali hydroxides.

Identification—Dissolve about 50 mg. of Phenprocoumon in 2 ml. of chloroform in a test tube, and add a few drops of pyridine and 0.5 ml. of a saturated solution of ferric chloride in chloroform, freshly prepared and filtered: an intense, bluish violet color is produced.

Melting range, page 814—Phenprocoumon melts between 177° and 181°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Phenprocoumon, previously dried in vacuum over phosphorus pentoxide at 100° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Phenprocoumon Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Phenprocoumon in 1 *N* alcoholic hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Phenprocoumon Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance occurring at about 311 mμ, do not differ by more than 3 percent.

Acidity—Transfer 1.0 g. of Phenprocoumon to a suitable flask, add 20 ml. of water, heat on a steam bath with constant stirring for 1 minute, and filter: the filtrate requires for neutralization not more than 0.5 ml. of 0.01 *N* sodium hydroxide, methyl red T.S. being used as the indicator.

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* Patented. See notice, page ii.

Loss on drying, page 814—Dry Phenprocoumon in vacuum over phosphorus pentoxide at 100° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Phenprocoumon yields not more than 0.1 percent of residue on ignition.

Salicylic acid—Add 25 ml. of water to 100 mg. of Phenprocoumon. Heat on a steam bath for 10 minutes, cool to room temperature, and filter into one of two matched color-comparison tubes, rinsing the filter with water. Adjust the volume to 49 ml. with water. To the second tube add 48 ml. of water and 1 ml. of a standard solution containing 100 mcg. of salicylic acid per ml. To each tube add 1 ml. of a freshly prepared solution of ferric ammonium sulfate, prepared by adding 1 ml. of 1 *N* hydrochloric acid to 2 ml. of ferric ammonium sulfate T.S. and diluting to 100 ml. Mix the contents of each tube: the color in the tube containing the sample is not more intense than that in the tube containing the standard, indicating not more than 0.1 percent of salicylic acid.

Assay—Transfer about 300 mg. of Phenprocoumon, accurately weighed, to a 100-ml. beaker, dissolve in 40 ml. of methanol, and add 10 ml. of water gradually with continued stirring. Immediately titrate with 0.1 *N* sodium hydroxide, determining the end-point potentiometrically using a calomel-glass electrode system. During the titration wash down with small portions of methanol the phenprocoumon which may migrate up the sides of the beaker. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 28.03 mg. of $C_{18}H_{16}O_3$.

Packaging and storage—Preserve Phenprocoumon in well-closed containers.

CATEGORY—Anticoagulant.

USUAL DOSE RANGE—Initial, **21 mg.** the first day, **9 mg.** the second day, and **3 mg.** the third day. Maintenance, **1 to 4 mg.,** daily according to prothrombin level.

Phenprocoumon Tablets

Phenprocoumon Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{18}H_{16}O_3$.

Identification—Extract a portion of finely powdered Phenprocoumon Tablets, equivalent to about 30 mg. of phenprocoumon, with 50 ml. of chloroform, and filter until clear. Evaporate the clear filtrate to dryness on a steam bath, and dry the residue at 105° for 30 minutes. The infrared absorption spectrum of a potassium bromide dispersion of the phenprocoumon so obtained exhibits maxima only at the same wavelengths as that of NF Phenprocoumon Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Phenprocoumon Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Phenprocoumon Tablets meet the requirements of the content uniformity test for tablets using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask, and add 50 ml. of 1 *N* alcoholic hydrochloric acid. Heat the flask on a steam bath for 30 minutes with occasional swirling, then cool, dilute to volume with 1 *N* alcoholic hydrochloric acid, and filter, discarding the first 25 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with 1 *N* alcoholic hydrochloric acid to provide a solution containing approximately 10 mcg. of phenprocoumon per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Phenprocoumon Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 311 mμ, with a suitable spectrophotometer, using 1 *N* alcoholic hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{18}H_{16}O_3$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of phenprocoumon in the tablet; D is the exact concentration, in mcg. per ml., of phenprocoumon in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Phenprocoumon Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 10 mg. of phenprocoumon, to a suitable flask, add about 25 ml. of chloroform, and heat on a steam bath near the boiling temperature for 10 minutes, with occasional swirling. Cool to room temperature, and filter through a suitable medium-porosity all-glass funnel into a suction flask. Rinse the flask with small portions of chloroform and add the rinsings to the all-glass funnel. Quantitatively transfer the filtrate to a

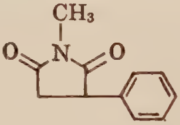
50-ml. volumetric flask, dilute to volume with chloroform, and mix. Extract 25.0 ml. of this solution with four 25-ml. portions of sodium hydroxide T.S. Combine the alkaline extracts in a 250-ml. separator, acidify with hydrochloric acid, and extract with four 25-ml. portions of chloroform. Wash the combined extracts with dilute hydrochloric acid (1 in 100), and filter the washed extract through chloroform-washed cotton into a 250-ml. volumetric flask. Extract the acid wash with 25 ml. of chloroform, and filter into the flask. Rinse the filter with chloroform, collecting the filtrate in the flask, then dilute to volume with chloroform, and mix. Transfer 25.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Phenprocoumon Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 311 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{18}H_{16}O_3$ in the portion of the Tablets taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Phenprocoumon Tablets in well-closed containers.

Tablets available—Phenprocoumon Tablets usually available contain the following amount of phenprocoumon: 3 mg.

CATEGORY and DOSE—See Phenprocoumon.

Phensuximide*



N-Methyl-2-phenylsuccinimide

$C_{11}H_{11}NO_2$ Mol. wt. 189.22

Phensuximide contains not less than 97.0 percent and not more than 103.0 percent of $C_{11}H_{11}NO_2$, calculated on the anhydrous basis.

Description—Phensuximide occurs as a white to off-white, crystalline powder. It is odorless or has not more than a slight odor.

Solubility—Phensuximide is slightly soluble in water, is soluble in alcohol, and is very soluble in chloroform.

Melting range, page 814—Phensuximide melts between 68° and 74°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Phensuximide, previously dried in vacuum at 50° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Phensuximide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2500 solution of Phensuximide in alcohol exhibits maxima and minima at the same wavelengths as that of NF Phensuximide Reference Standard, similarly measured.

Residue on ignition, page 858—Phensuximide yields not more than 0.5 percent of residue on ignition.

Water, page 900—Determine the water content of Phensuximide by the titrimetric method: not more than 1 percent is found.

Cyanide—Dissolve 1 g. of Phensuximide in 10 ml. of warm alcohol, and add 3 drops of ferrous sulfate T.S., 1 ml. of sodium hydroxide T.S., and a few drops of ferric chloride T.S. Warm gently, and finally acidify with diluted sulfuric acid: no blue precipitate or blue color is formed within 15 minutes.

Assay—Transfer about 200 mg. of Phensuximide, accurately weighed, to a 50-ml. volumetric flask. Dissolve in 40 ml. of alcohol, dilute to volume with alcohol, and mix. Transfer 5.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbances of this solution and of a solution of NF Phensuximide Reference Standard, in the same medium at a concentration of about 400 mcg. per ml., in 1-cm. cells, at the point of maximum absorbance at about 258 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{11}H_{11}NO_2$ in the Phensuximide taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Phensuximide in tight containers.

CATEGORY—Anticonvulsant.

USUAL DOSE RANGE—**500 mg.** to **1 g.** two or three times a day, irrespective of age.

Phensuximide Capsules

Phensuximide Capsules contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{11}H_{11}NO_2$.

Identification—The contents of Phensuximide Capsules meet the requirements for *Infrared absorption* under *Phensuximide*, page 546.

Weight variation, page 901—Phensuximide Capsules meet the requirements of the weight variation test for capsules.

Assay—Transfer, as completely as possible, the contents of not less than 20 Phensuximide Capsules to a suitable tared container, and weigh. Mix thoroughly with a glass rod. Weigh accurately a portion of the powder, equivalent to about 200 mg. of phensuximide, and transfer to a 125-ml. separator. Add 20 ml. of water, and extract with three 40-ml. portions of chloroform, filtering each successive chloroform extract through a chloroform-washed pledget of cotton into a 150-ml. extraction flask. Evaporate the combined chloroform extracts on a steam bath to about 3 ml., then allow the remaining chloroform to evaporate at room temperature. Dissolve the residue of phensuximide in 20 ml. of alcohol, transfer quantitatively to a 50-ml. volumetric flask, and dilute to volume with alcohol. Pipet 5.0 ml. of this solution into a 50-ml. volumetric flask, dilute to volume with alcohol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Phensuximide Reference Standard, in the same medium at a concentration of about 400 mcg. per ml., in 1-cm. cells, at the maximum at about 258 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg., of $C_{11}H_{11}NO_2$ in the portion of the Capsules taken by the formula $0.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Phensuximide Capsules in tight containers.

Capsules available—Phensuximide Capsules usually available contain the following amounts of phensuximide: 250 and 500 mg.

CATEGORY and DOSE—See Phensuximide.

Phensuximide Oral Suspension

Phensuximide Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{11}NO_2$.

Identification—Transfer a portion of Phensuximide Oral Suspension, equivalent to about 1 g. of phensuximide, to a separator. Add 50 ml. of water, and extract the suspension with 50 ml. of chloroform. Filter the chloroform layer, through chloroform-washed cotton, and evaporate in a current of warm air. Dissolve the residue in 5 ml. of alcohol, and add slowly, with stirring, 25 ml. of water. Allow the mixture to stand for about 15 minutes, filter, wash the precipitate well with water, and dry in vacuum at 50° for 4 hours. The residue so obtained meets the requirements for *Infrared absorption* under *Phensuximide*, page 546.

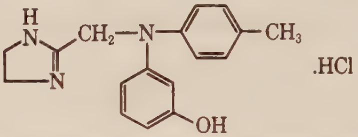
Assay—Transfer to an 800-ml. Kjeldahl flask an accurately measured volume of Phensuximide Oral Suspension, equivalent to about 625 mg. of phensuximide. Add about 350 ml. of water, several glass beads, a small amount of a silicone antifoam agent, and 30 g. of sodium hydroxide. Immediately connect the flask, by means of a distillation trap, to a well-cooled condenser that dips into 40 ml. of boric acid solution (1 in 25), and distil until about 250 ml. of distillate has been collected. Add 6 drops of methyl red-methylene blue T.S., and titrate with 0.1 N sulfuric acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N sulfuric acid is equivalent to 18.92 mg. of $C_{11}H_{11}NO_2$.

Packaging and storage—Preserve Phensuximide Oral Suspension in tight containers.

Suspension available—Phensuximide Oral Suspension usually available contains the following amount of phensuximide: 62.5 mg. per ml.

CATEGORY and DOSE—See Phensuximide.

Phentolamine Hydrochloride



m-[*N*-(2-Imidazolin-2-ylmethyl)-*p*-toluidino]phenol Monohydrochloride

$C_{17}H_{19}N_3O.HCl$ Mol. wt. 317.82

Phentolamine Hydrochloride, dried at 60° in vacuum for 2 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{17}H_{19}N_3O.HCl$.

Description—Phentolamine Hydrochloride occurs as a white or slightly grayish, crystalline, odorless powder. Its solutions are acid to litmus, having a pH of about 5, and foam on shaking.

Solubility—Phentolamine Hydrochloride is sparingly soluble in water and is slightly soluble in alcohol. It is very slightly soluble in chloroform and in ether.

Identification—

A: A solution of Phentolamine Hydrochloride (1 in 500) yields precipitates with iodine T.S., mercuric-potassium iodide T.S., trinitrophenol T.S., and ammonium reineckate T.S.

B: The phentolamine trichloroacetate obtained in the *Assay* melts between 136° and 141°, page 814.

C: Phentolamine Hydrochloride responds to the tests for *Chloride*, page 808.

Melting range, *Class Ia*, page 815—Phentolamine Hydrochloride melts between 238° and 242°.

Loss on drying, page 814—Dry Phentolamine Hydrochloride at 60° in vacuum for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Phentolamine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Weigh accurately about 150 mg. of Phentolamine Hydrochloride, previously dried at 60° in vacuum for 2 hours, transfer to a beaker, and dissolve in 20 ml. of water. Slowly add to the solution, while stirring, 30 ml. of trichloroacetic acid solution (1 in 10), and allow to stand for 2 hours. Collect the precipitate of phentolamine trichloroacetate with suction on a tared, sintered-glass crucible, transferring any precipitate adhering to the beaker with small portions of the trichloroacetic acid solution. Wash the precipitate with five 3-ml. portions of water, and dry it in vacuum over phosphorus pentoxide to constant weight. The weight of the phentolamine trichloroacetate so obtained, multiplied by 0.7146, represents the weight of $C_{17}H_{19}N_3O.HCl$ in the Phentolamine Hydrochloride taken.

Packaging and storage—Preserve Phentolamine Hydrochloride in well-closed, light-resistant containers.

CATEGORY—Antiadrenergic.

USUAL DOSE—**50 mg.** four to six times a day.

USUAL DOSE RANGE—**50** to **100 mg.**

Phentolamine Hydrochloride Tablets

Phentolamine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{17}N_{19}N_3O.HCl$.

Identification—The phentolamine trichloroacetate obtained in the *Assay* melts between 136° and 141°, page 814.

Disintegration, page 878—The disintegration time limit for Phentolamine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Phentolamine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Phentolamine Hydrochloride

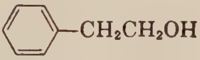
Tablets. Transfer to a small beaker an accurately weighed portion of the powder, equivalent to about 150 mg. of phentolamine hydrochloride, add 20 ml. of water, stir well, and allow to stand for 30 minutes, stirring frequently. Filter with suction, wash with four 5-ml. portions of water, and proceed as directed in the *Assay* under *Phentolamine Hydrochloride,* page 548, beginning with "Slowly add to the solution . . . ."

Packaging and storage—Preserve Phentolamine Hydrochloride Tablets in well-closed containers.

Tablets available—Phentolamine Hydrochloride Tablets usually available contain the following amount of phentolamine hydrochloride: 50 mg.

CATEGORY and DOSE—See Phentolamine Hydrochloride.

Phenylethyl Alcohol



Phenethyl Alcohol

$C_8H_{10}O$ Mol. wt. 122.17

Description—Phenylethyl Alcohol occurs as a colorless liquid with a rose-like odor and a sharp, burning taste.

Solubility—Phenylethyl Alcohol is soluble in water. It is very soluble in alcohol, in fixed oils, in glycerin, and in propylene glycol, and is slightly soluble in mineral oil.

Identification—Transfer 1 ml. of Phenylethyl Alcohol to a dry test tube, add 0.5 ml. of phenyl isocyanate (*Caution: phenyl isocyanate is a strong lacrimator*), and heat on a steam bath for 5 minutes. Cool, using ice if necessary, and induce crystallization by scratching the walls of the tube with a glass rod. After crystals have formed, add about 10 ml. of solvent hexane, heat to boiling for a few minutes, and filter the solution into a warm, dry test tube. Collect the crystals that form on a filter and wash them with cool solvent hexane. The crystals of phenethyl carbanilate so obtained melt between 78° and 80°, page 814.

Specific gravity, page 866—The specific gravity of Phenylethyl Alcohol is not less than 1.017 and not more than 1.020.

Refractive index, page 858—The refractive index of Phenylethyl Alcohol is not less than 1.531 and not more than 1.534 at 20°.

Residue on ignition, page 858—Evaporate 10 ml. of Phenylethyl Alcohol in a suitable crucible and ignite to constant weight: the weight of the residue is negligible.

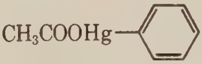
Chlorinated compounds—Wind a strip of 20-mesh copper gauze 1.5 cm. wide and 5 cm. long around the end of a copper wire. Heat the gauze in the nonluminous flame of a Bunsen burner until it glows without coloring the flame green. Permit the gauze to cool and re-heat several times until a good coat of oxide has formed. Apply with a medicine dropper, 2 drops of Phenylethyl Alcohol to the cooled gauze, ignite, and permit it to burn freely in the air. Again cool the gauze and add 2 more drops of Phenylethyl Alcohol and burn as before. Continue this process until a total of 6 drops has been added and ignited, and then hold the gauze in the outer edge of the Bunsen flame, adjusted to a height of about 4 cm.: not even a transient green color is imparted to the flame.

Aldehyde—Shake 5 ml. of Phenylethyl Alcohol with 5 ml. of sodium hydroxide T.S., and allow to stand for 1 hour: no yellow color appears in the water layer.

Packaging and storage—Preserve Phenylethyl Alcohol in tight, light-resistant containers in a cool, dry place.

CATEGORY—Bacteriostatic; preservative.

Phenylmercuric Acetate



Acetoxyphenylmercury

$C_8H_8HgO_2$ Mol. wt. 336.74

Phenylmercuric Acetate contains not less than 98.0 percent and not more than 100.5 percent of $C_8H_8HgO_2$.

Description—Phenylmercuric Acetate occurs as a white to creamy white, crystalline powder or as small white prisms or leaflets. It is odorless.

Solubility—Phenylmercuric Acetate is slightly soluble in water. It is soluble in alcohol and in acetone.

Identification—

A: Add 0.5 ml. of nitric acid to 100 mg. of Phenylmercuric Acetate, warm gently until a dark brown color is produced, and dilute to 10 ml. with water: the characteristic odor of nitrobenzene is evolved.

B: To 100 mg. of Phenylmercuric Acetate add 0.5 ml. of sulfuric acid and 1 ml. of alcohol, and warm: the characteristic odor of ethyl acetate is evolved.

C: To 5 ml. of a saturated solution of Phenylmercuric Acetate in water add a few drops of sodium sulfide T.S.: a white precipitate is formed, which turns black when the mixture is boiled and then allowed to stand.

Melting range, page 814—Phenylmercuric Acetate melts between 149° and 153°.

Residue on ignition, page 858—Phenylmercuric Acetate yields not more than 0.2 percent of residue on ignition.

Mercuric salts and heavy metals—Heat 100 mg. of Phenylmercuric Acetate with 15 ml. of water, cool, and filter. To the filtrate add a few drops of sodium sulfide T.S.: no immediate color is produced.

Polymercurated benzene compounds—Shake 2.0 g. of Phenylmercuric Acetate with 100 ml. of acetone, and filter. Wash the residue with successive portions of acetone until a total of 50 ml. is used, then dry the residue at 105° for 1 hour, and weigh: the weight of the residue does not exceed 30 mg. (1.5 percent).

Assay—Transfer about 500 mg. of Phenylmercuric Acetate, accurately weighed, to a 100-ml. flask, add 15 ml. of water, 5 ml. of formic acid, and 1 g. of zinc dust, and reflux for 30 minutes. Cool, filter, and wash the filter paper and the amalgam with water until the washings are no longer acid to litmus. Dissolve the amalgam in 40 ml. of dilute nitric acid (1 in 2). Heat on a steam bath for 3 minutes, then add 500 mg. of urea and enough potassium permanganate T.S. to produce a permanent pink color. Cool, decolorize the solution with hydrogen peroxide T.S., add 1 ml. of ferric ammonium sulfate T.S., and titrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* ammonium thiocyanate is equivalent to 16.84 mg. of $C_8H_8HgO_2$.

Packaging and storage—Preserve Phenylmercuric Acetate in tight, light-resistant containers.

CATEGORY—Preservative (bacteriostatic).

Phenylmercuric Nitrate

Phenylmercuric Nitrate is a mixture of phenylmercuric nitrate and phenylmercuric hydroxide containing not less than 87.0 percent and not more than 87.9 percent of $C_6H_5Hg^-$(phenylmercuric ions), and not less than 62.75 percent and not more than 63.50 percent of Hg (mercury).

Description—Phenylmercuric Nitrate occurs as a white, crystalline powder. It is affected by light. Its saturated solution is acid to litmus.

Solubility—Phenylmercuric Nitrate is very slightly soluble in water. It is slightly soluble in alcohol and in glycerin. It is more soluble in the presence of either nitric acid or alkali hydroxides.

Identification—

A: Add 3 ml. of sulfuric acid to 100 mg. of Phenylmercuric Nitrate: the mixture becomes yellow and the characteristic odor of nitrobenzene is evolved.

B: To 5 ml. of a saturated solution of Phenylmercuric Nitrate add 1 ml. of diluted hydrochloric acid: a white precipitate is formed.

C: To 5 ml. of a saturated solution of Phenylmercuric Nitrate add 5 ml. of ammonium sulfide T.S.: there is no reaction in the cold, but upon heating for 10 minutes in a boiling water bath a black precipitate is formed.

Melting range, page 814—Phenylmercuric Nitrate melts between 175° and 185°.

Residue on ignition, page 858—Phenylmercuric Nitrate yields not more than 0.1 percent of residue on ignition.

Mercury ions—To 5 ml. of a saturated solution of Phenylmercuric Nitrate, add 5 ml. of sodium hydroxide T.S.: no yellow precipitate is formed (*mercuric ions*) and the solution does not darken (*mercurous ions*).

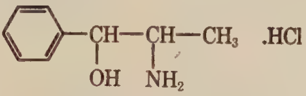
Assay for phenylmercuric ions—Transfer about 200 mg. of Phenylmercuric Nitrate, accurately weighed, to a conical flask and dissolve in 90 ml. of water and 10 ml. of nitric acid. Add 2 ml. of ferric ammonium sulfate T.S., and titrate with 0.05 *N* ammonium thiocyanate. Each ml. of 0.05 *N* ammonium thiocyanate is equivalent to 13.88 mg. of $C_6H_5Hg^-$ (phenylmercuric ions).

Assay for mercury—Transfer about 400 mg. of Phenylmercuric Nitrate, accurately weighed, into a 100-ml. flask, add 15 ml. of water, 5 ml. of formic acid, and 1 g. of zinc dust, and reflux for 30 minutes. Cool, filter, and wash the filter paper and the amalgam with water until the washings are no longer acid to litmus. Dissolve the amalgam in 40 ml. of dilute nitric acid (1 in 2). Heat on a steam bath for 3 minutes, then add 500 mg. of urea and enough potassium permanganate T.S. to produce a permanent pink color. Cool, decolorize the solution with hydrogen peroxide T.S., add 1 ml. of ferric ammonium sulfate T.S., and titrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* ammonium thiocyanate is equivalent to 10.03 mg. of Hg.

Packaging and storage—Preserve Phenylmercuric Nitrate in tight, light-resistant containers.

CATEGORY—Bacteriostatic.

Phenylpropanolamine Hydrochloride



(±)-Norephedrine Hydrochloride

$C_9H_{13}NO.HCl$ Mol. wt. 187.67

Phenylpropanolamine Hydrochloride contains not less than 95.0 percent and not more than 100.5 percent of $C_9H_{13}NO.HCl$, calculated on the dried basis.

Description—Phenylpropanolamine Hydrochloride occurs as a white, crystalline powder having a slight aromatic odor. It is affected by light.

Solubility—Phenylpropanolamine Hydrochloride is freely soluble in water and in alcohol. It is insoluble in ether.

Identification—Dissolve 500 mg. of Phenylpropanolamine Hydrochloride in 15 ml. of water, add 5 ml. of saturated sodium carbonate solution, and extract with two 10-ml. portions of chloroform. Wash the combined chloroform extracts with two 10-ml. portions of water, discard the washings, and transfer the chloroform solution to a small beaker. Evaporate most of the chloroform on a steam bath using a stream of air, then evaporate the last few ml. using the stream of air alone, and dry the crystals at 80° for 1 hour: the α-hydroxy-β-aminopropylbenzene so obtained melts between 101° and 101.5° (page 814).

Loss on drying, page 814—Dry Phenylpropanolamine Hydrochloride at 105° for 2 hours: it loses not more than 1 percent of its weight.

Melting range, page 814—Phenylpropanolamine Hydrochloride melts between 190° and 194°.

Residue on ignition, page 858—Phenylpropanolamine Hydrochloride yields not more than 0.3 percent of residue on ignition.

pH, page 824—The pH of a solution of Phenylpropanolamine Hydrochloride (3 in 100) is between 4.2 and 5.5.

α-Aminopropiophenone—Transfer 2.5 g. of Phenylpropanolamine Hydrochloride to a 100-ml. volumetric flask, add 0.1 *N* hydrochloric acid to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of α-aminopropiophenone, in the same medium at a concentration of 100.0 mcg. per ml., in 1-cm. cells, at the maximum at about 285 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank: the absorbance of the sample solution does not exceed that of the standard solution (about 0.4 percent).

Heavy metals, page 806—Dissolve 200 mg. of Phenylpropanolamine Hydrochloride in 5 ml. of water, add 1 ml. of diluted acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Phenylpropanolamine Hydrochloride is 50 parts per million.

Assay—Dissolve about 500 mg. of Phenylpropanolamine Hydrochloride, accurately weighed, in 50 ml. of glacial acetic acid. Add 10 ml. of mercuric acetate T.S., 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 18.77 mg. of $C_9H_{13}NO.HCl$.

Packaging and storage—Preserve Phenylpropanolamine Hydrochloride in tight, light-resistant containers.

CATEGORY—Adrenergic (vasoconstrictor).

USUAL DOSE—**25** to **50 mg.** every 3 or 4 hours.

Phosphoric Acid

H_3PO_4 Mol. wt. 98.00

Phosphoric Acid contains not less than 85.0 percent and not more than 88.0 percent, by weight, of H_3PO_4.

Description—Phosphoric Acid is a colorless, odorless liquid of syrupy consistence. Its specific gravity is about 1.71.

Solubility—Phosphoric Acid is miscible with water and with alcohol.

Identification—Phosphoric Acid, carefully neutralized with sodium hydroxide T.S., using phenolphthalein T.S. as the indicator, responds to the tests for *Phosphate*, page 809.

Nitrate—Dilute Phosphoric Acid with 14 volumes of water, mix 5 ml. of the dilution with about 0.1 ml. of indigo carmine T.S., then add 5 ml. of sulfuric acid: the blue color is not discharged within 1 minute.

Phosphorous or hypophosphorous acid—Dilute Phosphoric Acid with 14 volumes of water. Gently warm 5 ml. of the dilution and add 2 ml. of silver nitrate T.S.: the mixture does not become brownish.

Sulfate—Dilute Phosphoric Acid with 90 volumes of water, and add 1 ml. of barium chloride T.S.: no precipitate is formed immediately.

Arsenic—A solution of 1.25 g. of Phosphoric Acid in water meets the requirements of the *Arsenic Test*, page 777 (8 parts per million As).

Alkali phosphates—Transfer 1 ml. of Phosphoric Acid to a graduated cylinder, and add 6 ml. of ether and 2 ml. of alcohol: no turbidity is produced.

Heavy metals, page 806—Dilute 3 ml. (5 g.) of Phosphoric Acid with sufficient water to make 50 ml. Mix 10 ml. of this dilution with 5.5 ml. of sodium hydroxide T.S., and add sufficient water to make 25 ml.: the heavy metals limit for Phosphoric Acid is 20 parts per million.

Assay—Weigh accurately about 1 g. of Phosphoric Acid in a tared, glass-stoppered flask, and dilute it to about 120 ml. with water. Add about 0.5 ml. of thymolphthalein T.S., and titrate with 1 *N* sodium hydroxide to the first appearance of a blue color. Perform a blank determination, and make any necessary correction. Each ml. of 1 *N* sodium hydroxide is equivalent to 49.00 mg. of H_3PO_4.

Packaging and storage—Preserve Phosphoric Acid in tight containers.

CATEGORY—Solvent.

Diluted Phosphoric Acid

Diluted Phosphoric Acid contains, in each 100 ml., not less than 9.5 g. and not more than 10.5 g. of H_3PO_4.

Diluted Phosphoric Acid may be prepared as follows:

Phosphoric Acid	**69 ml.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Mix the ingredients.

Description—Diluted Phosphoric Acid is a clear, colorless, odorless liquid. Its specific gravity is about 1.057.

Alkali phosphates—Evaporate 20 ml. of Diluted Phosphoric Acid on a steam bath to a weight of about 5 g. Cool, transfer 2 ml. to a graduated cylinder, and add 6 ml. of ether and 2 ml. of alcohol: no turbidity is produced.

Other tests—Diluted Phosphoric Acid, without further dilution, conforms to the tests for *Identification, Nitrate, Phosphorous or hypophosphorous acid,* and *Sulfate* under *Phosphoric Acid,* page 552.

Arsenic—A solution of 6.67 g. of Diluted Phosphoric Acid in water meets the requirements of the *Arsenic Test*, page 777 (1.5 parts per million As).

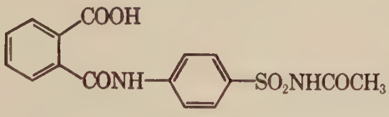
Heavy metals, page 806—Dilute 9.5 ml. (10 g.) of Diluted Phosphoric Acid with about 10 ml. of water, and add 6 ml. of sodium hydroxide T.S. and sufficient water to make 25 ml.: the heavy metals limit for Diluted Phosphoric Acid is 5 parts per million.

Assay—Pipet 10.0 ml. of Diluted Phosphoric Acid into a flask, and dilute it to about 50 ml. with water. Add 0.5 ml. of thymolphthalein T.S., and titrate with 1 *N* sodium hydroxide to the first appearance of a blue color. Perform a blank determination, and make any necessary correction. Each ml. of 1 *N* sodium hydroxide is equivalent to 49.00 mg. of H_3PO_4.

Packaging and storage—Preserve Diluted Phosphoric Acid in tight containers.

CATEGORY—See Phosphoric Acid.

Phthalylsulfacetamide



4′-(Acetylsulfamoyl)phthalanilic Acid

$C_{16}H_{14}N_2O_6S$ Mol. wt. 362.36

Phthalylsulfacetamide, dried at 105° for 4 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_{16}H_{14}N_2O_6S$.

Description—Phthalylsulfacetamide occurs as white or creamy white crystals or as a crystalline powder, possessing a slight odor. It decomposes with liquefaction between 186° and 202°.

Solubility—Phthalylsulfacetamide is very slightly soluble in water, soluble in acetone, and freely soluble in solutions of alkali hydroxides.

Identification—

A: To 100 mg. of Phthalylsulfacetamide in 10 ml. of water add dropwise, with stirring, sodium hydroxide T.S. until the Phthalylsulfacetamide is almost completely dissolved. Filter, and add to the filtrate a few drops of cupric sulfate T.S.: a light blue precipitate is formed.

B: To 100 mg. of Phthalylsulfacetamide, add 100 mg. of resorcinol, and heat the mixture slowly over an open flame until it melts and turns brick-red. Cool the mixture, add 35 ml. of sodium hydroxide T.S., and agitate to dissolve the melt: a greenish yellow fluorescence is produced.

C: To 100 mg. of Phthalylsulfacetamide add 100 mg. of phenol and 0.4 ml. of sulfuric acid. Heat the mixture slowly over an open flame until it melts and turns pink in color. Cool and add 20 ml. of sodium hydroxide T.S.: a deep red color is produced.

Acidity—To 2.4 g. of Phthalylsulfacetamide add 80 ml. of chilled water, stir, place the mixture in an ice bath for 5 minutes, and filter: 40 ml. of the filtrate require not more than 1.0 ml. of 0.1 *N* sodium hydroxide for neutralization, using 2 drops of phenolphthalein T.S. as indicator.

Residue on ignition, page 858—Phthalylsulfacetamide yields not more than 0.1 percent of residue on ignition.

Clarity and color of solution—A solution of 1 g. of Phthalylsulfacetamide in a mixture of 20 ml. of water and 10 ml. of sodium hydroxide T.S. is clear and is not more than slightly yellow.

Chloride, page 784—Digest 4 g. of Phthalylsulfacetamide in 100 ml. of water at 70° for 5 minutes, cool to room temperature, and filter. A 25-ml. portion of the filtrate shows no more chloride than corresponds to 0.2 ml. of 0.02 *N* hydrochloric acid (0.014 percent).

Sulfate, page 784—A 25-ml. portion of the filtrate prepared in the test for *Chloride* shows no more sulfate than corresponds to 0.4 ml. of 0.02 *N* sulfuric acid (0.04 percent).

Heavy metals, page 806—Dissolve 1 g. of Phthalylsulfacetamide in 5 ml. of sodium hydroxide T.S., and add 20 ml. of water and 5 drops of sodium sulfide T.S. Any darkening produced is not more than that obtained in a blank to which 2 ml. of standard lead solution has been added (20 parts per million).

Limit of free sulfacetamide—Weigh accurately 2.4 g. of Phthalylsulfacetamide, transfer to a beaker, add 40 ml. of 18 percent hydrochloric acid, add about 25 g. of crushed ice, and slowly titrate with 0.1 *M* sodium nitrite determining the end-point electrometrically using calomel and platinum electrodes. Not more than 0.3 ml. of 0.1 *M* sodium nitrite is required (0.27 percent).

Assay—Weigh accurately about 600 mg. of Phthalylsulfacetamide, previously dried at 105° for 4 hours, transfer it to a flask, add 20 ml. of hydrochloric acid and 50 ml. of water, and reflux for 30 minutes. Transfer the contents of the flask to a beaker with the aid of 20 ml. of hydrochloric acid and 50 ml. of water, cool to 15°, and titrate slowly with 0.1 *M* sodium nitrite, determining the end-point electrometrically, using calomel and platinum electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 36.24 mg. of $C_{16}H_{14}N_2O_6S$.

Packaging and storage—Preserve Phthalylsulfacetamide in well-closed, light-resistant containers.

CATEGORY—Antibacterial (intestinal).
USUAL DOSE—**2 g.** three times a day.
USUAL DOSE RANGE—**1.5** to **4 g.**

Phthalylsulfacetamide Tablets

Phthalylsulfacetamide Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{16}H_{14}N_2O_6S$.

Identification—Triturate a quantity of finely powdered Phthalylsulfacetamide Tablets, equivalent to about 1.5 g. of phthalylsulfacetamide, with 50 ml. of acetone, filter, and evaporate the filtrate to dryness on a steam bath. The phthalylsulfacetamide so obtained responds to the *Identification tests* under *Phthalylsulfacetamide*, page 553.

Disintegration, page 878—The disintegration time limit for Phthalylsulfacetamide Tablets is 15 minutes.

Weight variation, page 901—Phthalylsulfacetamide Tablets meet the requirements of the weight variation test for tablets.

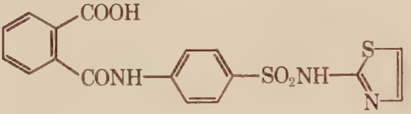
Assay—Weigh and finely powder not less than 20 Phthalylsulfacetamide Tablets. Weigh accurately a portion of the powder, equivalent to about 600 mg. of Phthalylsulfacetamide, transfer it to a flask, add 20 ml. of hydrochloric acid and 50 ml. of water, and proceed as directed in the *Assay* under *Phthalylsulfacetamide*, page 553, beginning with ". . . and reflux for 30 minutes. . . ."

Packaging and storage—Preserve Phthalylsulfacetamide Tablets in well-closed, light-resistant containers.

Tablets available—Phthalylsulfacetamide Tablets usually available contain the following amount of phthalylsulfacetamide: 500 mg.

CATEGORY and DOSE—See Phthalylsulfacetamide.

Phthalylsulfathiazole



4′-(2-Thiazolylsulfamoyl)phthalanilic Acid

$C_{17}H_{13}N_3O_5S_2$ Mol. wt. 403.44

Phthalylsulfathiazole contains not less than 98.0 percent and not more than 100.5 percent of $C_{17}H_{13}N_3O_5S_2$, calculated on the dried basis.

Description—Phthalylsulfathiazole occurs as a white or faintly yellowish white, odorless crystalline powder, having a slightly bitter taste. It may darken on long exposure to light. It melts, with decomposition, at about 275°, as determined by the procedure for *Class Ia*, page 815.

Solubility—Phthalylsulfathiazole is practically insoluble in water and in chloroform, and is slightly soluble in alcohol. It is very slightly soluble in ether, and is soluble in solutions of alkali hydroxides and carbonates, and in hydrochloric acid.

Identification—

A: To 250 mg. of Phthalylsulfathiazole add 500 mg. of sodium bicarbonate and 10 ml. of water, and warm: the Phthalylsulfathiazole dissolves and carbon dioxide is evolved.

B: Mix about 20 mg. of Phthalylsulfathiazole with about 20 mg of resorcinol in a test tube, add 0.5 ml. of sulfuric acid, and heat in an oil bath at 160° for 3 minutes. Cool, and pour the solution into a mixture of 10 ml. of sodium hydroxide solution (1 in 10) and 200 ml. of water: the liquid acquires a yellow color by transmitted light and shows a vivid green fluorescence, which disappears when the solution is acidified and reappears when it is again made alkaline. Add 0.5 ml. of bromine T.S. to 10 ml. of the fluorescent solution: the solution is pink by transmitted light but retains the green fluorescence.

Acidity—Mix 2 g. of Phthalylsulfathiazole with 100 ml. of water, allow to stand for 30 minutes, shaking frequently, and filter. To 25 ml. of the filtrate add phenolphthalein T.S., and titrate with 0.02 *N* sodium hydroxide: not more than 5 ml. is required for neutralization.

Loss on drying, page 814—Dry Phthalylsulfathiazole at 105° for 4 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Phthalylsulfathiazole yields not more than 0.1 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 200 mg. of Phthalylsulfathiazole meets the requirement of the *Selenium Limit Test,* page 865 (30 parts per million).

Heavy metals—Dissolve 500 mg. of Phthalylsulfathiazole in a mixture of 5 ml. of sodium hydroxide T.S. and 20 ml. of water, and to the solution add 5 drops of sodium sulfide T.S.: any darkening produced is not greater than that in a blank made with the same quantities of the same reagents and to which 1 ml. of standard ead solution (see page 806) has been added (20 parts per million).

Assay—Transfer about 1 g. of Phthalylsulfathiazole, accurately weighed, to a small flask, add 20 ml. of hydrochloric acid and 10 ml. of water, and reflux for 1 hour. Transfer to a beaker or a casserole with the aid of about 40 ml. of water, cool to 15°, and slowly titrate with 0.1 *M* sodium nitrite until a blue color is produced immediately when the titrated solution is spotted on starch iodide paper. When the titration is complete, the endpoint is reproducible after the mixture has been allowed to stand for 5 minutes. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 40.34 mg. of $C_{17}H_{13}N_3O_5S_2$.

Packaging and storage—Preserve Phthalylsulfathiazole in well-closed, light-resistant containers.

CATEGORY—Antibacterial (intestinal).

USUAL DOSE—**1 g.** every 4 hours.

USUAL DOSE RANGE—**4** to **12 g.** daily.

Phthalylsulfathiazole Tablets

Phthalylsulfathiazole Tablets contain not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{17}H_{13}N_3O_5S_2$.

Identification—Triturate a finely powdered Phthalylsulfathiazole Tablet with two 5-ml. portions of chloroform, and discard the chloroform. Triturate the residue with 10 ml. of ammonia T.S. for 5 minutes, add 10 ml. of water, and filter. Warm the filtrate until most of the ammonia is expelled, cool, and add acetic acid until the reaction is distinctly acid: a precipitate of phthalylsulfathiazole is formed and, when collected on a filter, washed well with cold water, and dried at 105° for 1 hour, it responds to the *Identification tests* and meets the requirements for melting temperature in the *Description* under *Phthalylsulfathiazole,* page 554.

Disintegration, page 878—The disintegration time limit for Phthalylsulfathiazole Tablets is 30 minutes.

Weight variation, page 901—Phthalylsulfathiazole Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Phthalylsulfathiazole Tablets. Weigh accurately a portion of the powder, equivalent to about 1 g. of phthalylsulfathiazole, add 20 ml. of hydrochloric acid and 10 ml. of water, and reflux for 1 hour. Transfer to a beaker or a casserole with the aid of about 40 ml. of water, cool to 15°, and proceed as directed in the *Assay* under *Phthalylsulfathiazole,* page 554, beginning with "and slowly titrate. . . ."

Packaging and storage—Preserve Phthalylsulfathiazole Tablets in well-closed, light-resistant containers.

Tablets available—Phthalylsulfathiazole Tablets usually available contain the following amount of phthalylsulfathiazole: 500 mg.

CATEGORY and DOSE—See Phthalylsulfathiazole.

Picrotoxin

$C_{30}H_{34}O_{13}$ Mol. wt. 602.60

Picrotoxin is an active principle obtained from the seed of *Anamirta cocculus* (Linné) Wight et Arnott (Fam. *Menispermaceæ*).

Description—Picrotoxin occurs as flexible, shining, prismatic crystals or as a microcrystalline powder. It is odorless, and stable in air, but is affected by light. Its solutions are neutral to litmus.

Solubility—Picrotoxin is slightly soluble in water and is soluble in boiling water. It is freely soluble in boiling alcohol. It is more readily soluble in diluted acids and alkalies. It is sparingly soluble in ether and in chloroform.

Identification—

A: To Picrotoxin add sulfuric acid: a golden-yellow solution is produced which changes gradually to reddish brown.

B: Mix about 200 mg. of potassium nitrate with 3 or 4 drops of sulfuric acid in a suitable porcelain dish. Sprinkle a few particles of Picrotoxin on the mixture, and add sodium hydroxide solution (1 in 4), dropwise, until it is in excess: the particles of Picrotoxin acquire a red color which gradually fades.

C: Dilute 2 ml. of alkaline cupric tartrate T.S. with 10 ml. of water, and add a few particles of Picrotoxin: a red precipitate forms slowly in the cold, but rapidly upon boiling.

Melting range, page 814—Picrotoxin melts between 198° and 200°.

Residue on ignition, page 858—The residue on ignition from 200 mg. of Picrotoxin is negligible.

Alkaloids—A saturated solution of Picrotoxin yields no precipitate with platinic chloride T.S., tannic acid T.S., or mercuric-potassium iodide T.S.

Packaging and storage—Preserve Picrotoxin in well-closed, light-resistant containers.

CATEGORY—Central and respiratory stimulant.

USUAL DOSE—Intravenous. To be determined by the physician according to the needs of the patient.

Picrotoxin Injection

Picrotoxin Injection is a sterile solution of picrotoxin in isotonic sodium chloride solution. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{30}H_{34}O_{13}$.

Alcohol or chlorobutanol may be added to Picrotoxin Injection as a preservative.

Identification—

A: The picrotoxin obtained in the *Assay* melts between 197° and 200°, page 814, and responds to the *Identification tests* under *Picrotoxin,* page 555.

B: Picrotoxin Injection responds to the tests for *Sodium,* page 810, and for *Chloride,* page 808.

Sodium chloride content—Pipet 10.0 ml. of Picrotoxin Injection into a glass-stoppered conical flask, and add 25 ml. of water. Add slowly, while agitating, 25.0 ml. of 0.1 *N* silver nitrate, then add 3 ml. of nitric acid and 3 ml. of nitrobenzene, and shake well. Add 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 5.844 mg. of NaCl. Not less than 850 mg. and not more than 950 mg. of NaCl is present in 100 ml. of the Injection.

Other requirements—Picrotoxin Injection meets the requirements under *Injections,* page 810.

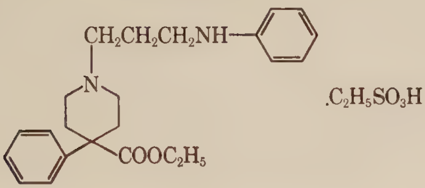
Assay—Transfer to a separator an accurately measured volume of Picrotoxin Injection, equivalent to about 50 mg. of picrotoxin. If the Injection contains alcohol, first evaporate sufficiently to expel the alcohol and then transfer completely to the separator. Add 1 ml. of diluted hydrochloric acid, and extract the picrotoxin completely by shaking with several successive portions of chloroform, until 2 ml. of the last chloroform extract leaves no weighable residue upon evaporation on a steam bath. Wash the combined chloroform extracts with two 10-ml. portions of water, slightly acidified with hydrochloric acid, then extract the combined water washings with 10 ml. of chloroform, and add it to the main chloroform solution. Evaporate the combined chloroform extracts on a steam bath in a tared vessel, dry at 105° for 2 hours, cool, and weigh. The weight so obtained represents the weight of $C_{30}H_{34}O_{13}$ in the volume of the Injection taken for the assay.

Packaging and storage—Preserve Picrotoxin Injection in single-dose or multiple-dose containers, preferably of Type I or Type III glass. Protect the Injection from light.

Injection available—Picrotoxin Injection usually available contains the following amount of picrotoxin: 3 mg. in 1 ml.

CATEGORY and DOSE—See Picrotoxin.

Piminodine Esylate*



Ethyl 1-(3-Anilinopropyl)-4-phenylisonipecotate Monoethanesulfonate

$C_{23}H_{30}N_2O_2 . C_2H_6O_3S$ Mol. wt. 476.64

Piminodine Esylate contains not less than 97.0 percent and not more than 100.5 percent of $C_{23}H_{30}N_2O_2 . C_2H_6O_3S$, calculated on the dried basis.

Description—Piminodine Esylate occurs as a colorless, crystalline solid having a slightly bitter taste. The pH of a 1 in 125 solution is about 4.8.

Solubility—Piminodine Esylate is slightly soluble in water and in ether. It is freely soluble in chloroform and in alcohol.

Identification—A solution of Piminodine Esylate (1 in 5000) in methanol exhibits an absorbance maximum at about 294 ± 2 mμ and a minimum at about 269 ± 2 mμ.

Melting range, page 814—Piminodine Esylate melts between 128° and 135°.

Loss on drying, page 814—Dry Piminodine Esylate to constant weight in vacuum at 70°: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Piminodine Esylate yields not more than 0.2 percent of residue on ignition.

Assay—Transfer about 130 mg. of Piminodine Esylate, accurately weighed, to a separator containing 25 ml. of water. Shake to dissolve the sample, add 0.5 ml. of sodium carbonate T.S., and extract successively with one 25-ml. portion, two 20-ml. portions, and one 10-ml. portion of ether. Wash the combined extracts with two 10-ml. portions of water, transfer the ether to a beaker, and evaporate just to dryness on a steam bath. If any water remains, add a few ml. each of dehydrated alcohol and ether, and evaporate again. Take up the residue in 20 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 23.83 mg. of $C_{23}H_{30}N_2O_2 . C_2H_6O_3S$.

Packaging and storage—Preserve Piminodine Esylate in tight, light-resistant containers.

CATEGORY—Analgesic (narcotic).

USUAL DOSE RANGE—Intramuscular and subcutaneous, **10** to **20 mg.** every 4 hours as needed depending on the degree of pain and the patient's response; oral, **25** to **50 mg.** every 4 to 6 hours.

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* Patented. See notice, page ii

Piminodine Esylate Injection

Piminodine Esylate Injection is a sterile solution of piminodine esylate in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{23}H_{30}N_2O_2 . C_2H_6O_3S$.

Identification—Dilute Piminodine Esylate Injection with methanol to produce a solution containing about 200 mcg. of piminodine esylate per ml.: this solution exhibits an ultraviolet absorbance maximum at 294 ± 2 mμ and a minimum at 269 ± 2 mμ.

pH, page 824—The pH of Piminodine Esylate Injection is between 3.8 and 4.8.

Other requirements—Piminodine Esylate Injection meets the requirements under *Injections,* page 810.

Assay—Transfer an accurately measured volume of Piminodine Esylate Injection, equivalent to about 200 mg. of piminodine esylate, to a separator containing 25 ml. of water, add 1 ml. of sodium carbonate T.S., and extract with four 20-ml. portions of ether. Wash the combined extracts with two 15-ml. portions of water or until free of alkali. Quantitatively transfer the ether to a beaker, and evaporate just to dryness on a steam bath using low heat. If any water remains, add a few ml. each of dehydrated alcohol and ether, and evaporate again. Dissolve the residue in 20 ml. of glacial acetic acid, add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 23.83 mg. of $C_{23}H_{30}N_2O_2 . C_2H_6O_3S$.

Packaging and storage—Preserve Piminodine Esylate Injection in single-dose containers, preferably of Type I glass and protected from light.

Injection available—Piminodine Esylate Injection usually available contains the following amount of piminodine esylate: 20 mg. in 1 ml.

CATEGORY and DOSE—See Piminodine Esylate.

Piminodine Esylate Tablets

Piminodine Esylate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{23}H_{30}N_2O_2 . C_2H_6O_3S$.

Identification—Transfer an amount of finely powdered Piminodine Esylate Tablets, equivalent to about 40 mg. of piminodine esylate, to a 200-ml. volumetric flask, add methanol to volume, mix, and filter: this solution exhibits an ultraviolet absorbance maximum at 294 ± 2 mμ and a minimum at 269 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Piminodine Esylate Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Piminodine Esylate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask, add 50 ml. of methanol, and shake mechanically for 30 minutes. Dilute to volume with methanol, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with methanol to obtain a solution containing approximately 200 mcg. of piminodine esylate per ml. Concomitantly determine the absorbance of this solution and of a standard solution of NF Piminodine Esylate, in the same medium, at a concentration of about 200 mcg. per ml., in 1-cm. cells, at the maximum at about 294 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{23}H_{30}N_2O_2 . C_2H_6O_3S$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of piminodine esylate, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of piminodine esylate in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the standard solution.

Assay—Weigh and finely powder not less than 20 Piminodine Esylate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 250 mg. of piminodine esylate, to a 50-ml. volumetric flask, and add 25 ml. of water and sufficient 2 *N* hydrochloric acid to make the mixture acid. Add 1 ml. in excess of the 2 *N* hydrochloric acid, and dilute to volume with water. Shake mechanically for 5 minutes, and filter, discarding the first 10 ml. of filtrate. Transfer 25.0 ml. of the subsequent filtrate to a separator, add 10 ml. of sodium carbonate T.S., and continue as directed in the *Assay* under *Piminodine Esylate Injection*, page 557, beginning with "... extract with four 20-ml. portions of ether."

Packaging and storage—Preserve Piminodine Esylate Tablets in tight light-resistant containers.

Tablets available—Piminodine Esylate Tablets usually available contain the following amount of piminodine esylate: 50 mg.

CATEGORY and DOSE—See Piminodine Esylate.

Pine Needle Oil

Pine Needle Oil is the volatile oil distilled with steam from the fresh leaf of *Pinus mugo* Turra and its variety *pumilio* (Haenke) Zenari (Fam. *Pinaceæ*).

Pine Needle Oil contains not less than 3.0 percent and not more than 10.0 percent, by weight, of esters calculated as $C_{12}H_{20}O_2$ (bornyl acetate).

Description—Pine Needle Oil is a colorless or yellowish liquid, having a pleasant, aromatic odor, and a bitter, pungent taste.

Solubility—Pine Needle Oil dissolves in from 4.5 to 10 volumes of 90 percent alcohol, often with turbidity.

Specific gravity, page 866—The specific gravity of Pine Needle Oil is not less than 0.853 and not more than 0.871.

Angular rotation, page 822—The angular rotation of Pine Needle Oil is between −5° and −15.5° in a 100-mm. tube.

Refractive index, page 858—The refractive index of Pine Needle Oil is between 1.475 and 1.480 at 20°.

Distilling range, page 782—Less than 10 percent of Pine Needle Oil distils below 165°.

Assay—Place 10 ml. of Pine Needle Oil in a tared, 125-ml. conical flask, and weigh it accurately. Add 25.0 ml. of 0.5 *N* alcoholic potassium hydroxide, connect the flask with a reflux condenser, and boil the mixture on a steam bath for exactly 1 hour. Allow the mixture to cool, add 10 drops of phenolphthalein T.S., and titrate the excess alkali with 0.5 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations,* page 883). The number of ml. of 0.5 *N* alcoholic potassium hydroxide consumed in the saponification, multiplied by 0 09815, indicates the number of g. of esters, calculated as $C_{12}H_{20}O_2$, in the amount of the Oil taken for the assay.

Packaging and storage—Preserve Pine Needle Oil in tight containers.

CATEGORY—Perfume; flavor.

Pine Tar

Pine Tar is the product obtained by the destructive distillation of the wood of *Pinus palustris* Miller, or of other species of *Pinus* Linné (Fam. *Pinaceæ*).

Description—Pine Tar is a very viscid, blackish brown liquid. It is translucent in thin layers, but becomes granular and opaque with age. It has an empyreumatic, terebinthinate odor, a sharp, empyreumatic taste, and is denser than water. Its aqueous solution is acid to litmus.

Solubility—Pine Tar is miscible with alcohol, with ether, with chloroform, with glacial acetic acid, and with fixed and volatile oils. It is slightly soluble in water, the solution being pale yellow to yellowish brown.

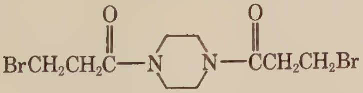
Identification—Shake about 1 ml. of Pine Tar with 10 ml. of water for 10 minutes, filter, and add 1 drop of ferric chloride T.S. to the filtrate: the mixture has a green color which rapidlychanges to brown.

Residue on ignition, page 858—Pine Tar yields not more than 0.3 percent of residue on ignition.

Packaging and storage—Preserve Pine Tar in tight containers.

CATEGORY—Local antieczematic; rubefacient.

Pipobroman*



1,4-Bis(3-bromopropionyl)piperazine

$C_{10}H_{16}Br_2N_2O_2$ Mol. wt. 356.06

Pipobroman contains not less than 98.0 percent and not more than 101.5 percent of $C_{10}H_{16}Br_2N_2O_2$, calculated on the dried basis.

Description—Pipobroman occurs as a white or practically white, crystalline powder, having a slightly sharp, fruity odor.

Solubility—Pipobroman is slightly soluble in water, sparingly soluble in alcohol, soluble in acetone, freely soluble in chloroform, and very slightly soluble in ether.

Identification—Dissolve 2 mg. of

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* Patented. See notice, page ii.

Pipobroman in 2 ml. of water, warming gently to effect solution. Add 2 ml. of hydroxylamine hydrochloride T.S. and 2 ml. of 3 N sodium hydroxide, mix, and allow to stand for 30 minutes. Acidify with diluted hydrochloric acid, and add 2 ml. of ferric chloride T.S.: a reddish-amber color is produced.

Melting range, page 814—Pipobroman melts between 101° and 105°.

Infrared absorption, page 866—The infrared absorption spectrum of a solution of Pipobroman, previously dried in vacuum at 60° for 4 hours, in chloroform (7 in 100) exhibits maxima only at the same wavelengths as that of NF Pipobroman Reference Standard, similarly measured.

Loss on drying, page 814—Dry Pipobroman in vacuum at 60° for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Pipobroman yields not more than 0.5 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Pipobroman is 20 parts per million.

Free bromide—Transfer about 1 g. of Pipobroman, accurately weighed, to a tall-form beaker, dissolve in 50 ml. of methanol, add 50 ml. of water, and acidify with diluted nitric acid. Titrate with 0.05 N silver nitrate, determining the end-point potentiometrically, using a glass-silver electrode system. Each ml. of 0.05 N silver nitrate is equivalent to 3.995 mg. of Br. Not more than 0.5 percent of free bromide is found.

Assay—Transfer about 200 mg. of Pipobroman, accurately weighed, to a 125-ml. conical flask, add 30 ml. of methanolic potassium hydroxide solution (1 in 200), attach a water condenser, and boil for 1 hour. Cool, transfer the solution to a tall-form beaker with the aid of 75 ml. of water, and acidify with 15 ml. of diluted nitric acid. Add 10 ml. of chlorobenzene, and titrate with 0.1 N silver nitrate, determining the end-point potentiometrically, using a glass-silver electrode system. Each ml. of 0.1 N silver nitrate is equivalent to 17.80 mg. of $C_{10}H_{16}Br_2N_2O_2$.

Packaging and storage—Preserve Pipobroman in well-closed containers.

CATEGORY—Antineoplastic.

USUAL DOSE RANGE—**1 to 3 mg. per kg.** of body weight daily, depending on condition being treated and patient response.

Pipobroman Tablets

Pipobroman Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{10}H_{16}Br_2N_2O_2$.

Identification—Reflux a portion of powdered Pipobroman Tablets, equivalent to about 15 mg. of pipobroman, with 75 ml. of acetone for 30 minutes, cool, and filter. Evaporate 10 ml. of the filtrate to dryness at a temperature not exceeding 70°, with the aid of a current of air: the residue responds to the *Identification test* under *Pipobroman*, page 559.

Disintegration, page 878—The disintegration time limit for Pipobroman Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Pipobroman Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Pipobroman Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg. of pipobroman, to a 125-ml. conical flask, add 30 ml. of methanolic potassium hydroxide solution (1 in 200), attach a water condenser, and boil for 1 hour. Cool, transfer the solution to a tall-form beaker with the aid of 75 ml. of water, acidify with 15 ml. of diluted nitric acid, and add 10 ml. of chlorobenzene. Titrate with 0.05 N silver nitrate, determining the end-point potentiometrically using a glass-silver electrode system. Each ml. of 0.05 N silver nitrate is equivalent to 8.902 mg. of $C_{10}H_{16}Br_2N_2O_2$.

Packaging and storage—Preserve Pipobroman Tablets in well-closed containers.

Tablets available—Pipobroman Tablets usually available contain the following amounts of pipobroman: 10 and 25 mg.

CATEGORY and DOSE—See Pipobroman.

Pituitary, Posterior, page 566
Pituitary, Posterior, Injection, page 567

Plantago Seed

Plantago Seed is the cleaned, dried, ripe seed of *Plantago psyllium* Linné, or of *Plantago indica* Linné (*Plantago arenaria* Waldstien et Kitaibel), known in commerce as Spanish or French Psyllium Seed; or of *Plantago ovata* Forskal, known in commerce as Blond Psyllium or Indian Plantago Seed (Fam. *Plantaginaceæ*).

Unground Plantago Seed—The seed of *Plantago psyllium* is ovate to ovate-elongate, concavo-convex; mostly from 1.3 to 2.7 mm. in length, rarely up to 3 mm., and from 0.6 to 1.1 mm. in width. It is light brown to moderate brown, darker along the margin, and very glossy; the convex dorsal surface exhibiting a lighter-colored longitudinal area extending nearly the length of the seed and representing the embryo lying beneath the seed coat, and showing a sometimes indistinct transverse groove nearer the broader end. The concave ventral surface has a deep cavity, in the center of the base of which is an oval, yellowish white hilum.

The seed of *Plantago indica* is ovate-oblong to elliptical, concavo-convex; from 1.6 to 3.0 mm. in length and from 1.0 to 1.5 mm. in width. Externally it is dark reddish brown to moderate yellowish brown, occasionally somewhat glossy, often dull, rough, and reticulate; the convex dorsal surface having a longitudinal lighter-colored area extending lengthwise along the center and beneath the seed coat, and a median transverse groove, dent, or fissure. The ventral surface has a deep concavity, the edges somewhat flattened and frequently forming a sharp indented angle with the base of the cavity, the latter showing a light-colored oval hilum.

The seed of *Plantago ovata* is broadly elliptical, to ovate, boat-shaped, from 2 to 3.5 mm. in length and from 1 to 1.5 mm. in width. It is pale brown to moderate brown with a dull surface, the convex surface having a small, elongated, glossy brown spot. The concave surface has a deep cavity, in the center of the base of which occurs a hilum covered with a thin membrane.

Odor and taste—All varieties of Plantago Seed are nearly odorless and have a bland mucilaginous taste.

Histology—Plantago Seed is reniform in median transverse sections. It shows a seed coat with a colorless epidermis of mucilaginous cells whose radial and outer walls break down to form layers of mucilage when brought into contact with water, and a reddish brown to yellow pigment layer in the seeds of *Plantago indica* and *Plantago psyllium* a broad endosperm with thick-walled outer palisade cells, and irregular inner endosperm cells; and a straight embryo extending lengthwise through the center. The endosperm and embryo cells contain fixed oil and aleurone grains, the latter being rounded, oval, pyriform, or irregularly shaped, from 2 to 8 μ in diameter.

Test for quality—Place 1 g. of Plantago Seed in a 25-ml. graduated cylinder, add water to the 20-ml. mark, and shake the cylinder at intervals during 24 hours; allow the seeds to settle for 12 hours and note the total volume occupied by the swollen seeds: the seeds of *Plantago psyllium* occupy a volume of not less than 14 ml., those of *Plantago ovata* not less than 10 ml., and those of *Plantago indica* not less than 8 ml.

Total ash, page 885—Plantago Seed yields not more than 4 percent of total ash.

Acid-insoluble ash, page 885—Plantago Seed yields not more than 1 percent of acid-insoluble ash.

Foreign organic matter, page 885—Plantago Seed contains not more than 0.5 percent of foreign organic matter.

CATEGORY—Cathartic.
USUAL DOSE—**7.5 g.**
USUAL DOSE RANGE—**4 to 15 g.**

Polycarbophil*

Polycarbophil is polyacrylic acid cross-linked with divinyl glycol.

Description—Polycarbophil occurs as white to creamy white granules. It has a characteristic, ester-like odor. It swells in water to a range of volumes depending primarily on the pH.

Solubility—Polycarbophil is insoluble in water, in dilute acids, in dilute alkalies, and in common organic solvents.

Identification—Polycarbophil, tested as described for test *B* under *Absorbing power*, absorbs about 60 times its original weight.

pH, page 824—To 1 g. of Polycarbophil, previously dried at 45° in vacuum for 4 hours, add 100 ml. of water, and shake mechanically for 1 hour: the pH of the mixture is not more than 4.0.

Loss on drying, page 814—Dry Polycarbophil at 45° in vacuum for 4 hours: it loses not more than 1.5 percent of its weight.

Residue on ignition, page 858—Polycarbophil yields not more than 4 percent of residue on ignition.

Water-soluble substances—To 1.5 g. of Polycarbophil add 200.0 ml. of water, shake mechanically for 6 hours, and then centrifuge. Filter the supernatant liquid through a fine-porosity sintered-glass funnel. Evaporate 100.0 ml. of the filtrate to dryness on a steam bath, and dry the residue to constant weight at 105°: the weight of the residue does not exceed 7.5 percent, calculated on the dried basis.

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* Patented. See notice, page ii.

Absorbing power—

A: Plug the tip of a 150-ml. sintered-glass, coarse-porosity filter funnel with a rubber stopper. Transfer 125 ml. of sodium bicarbonate solution (1.5 in 100) and 500 mg. of Polycarbophil to the funnel, cover the funnel with a watch glass, and allow to stand for 30 minutes. Remove the stopper and watch glass, and allow the liquid to drain for 10 minutes. Again plug the tip of the funnel, add an additional 100 ml. of the sodium bicarbonate solution, cover, and allow to stand for 4 hours. Remove the stopper and watch glass, and allow the liquid to drain for 45 minutes. Weigh the funnel with its contents. Discard the contents, wash the funnel thoroughly with water, and allow to drain for 10 minutes. Dry the outside of the funnel, and weigh. Calculate the weight of solution absorbed by the Polycarbophil: 1 g. of Polycarbophil absorbs not less than 62 g. of the sodium bicarbonate solution.

B: Repeat the test described under *A*, except replace the two portions of sodium bicarbonate solution with equal portions of pH 8.0 solution, made by mixing 291.75 ml. of 0.2 *M* dibasic sodium phosphate, 8.25 ml. of 0.1 *M* citric acid, and 30 mg. of thymol: 1 g. of Polycarbophil absorbs not less than 31 g. of pH 8.0 solution.

C: Repeat the test described under *A*, except replace the two portions of sodium bicarbonate solution with equal portions of pH 8.0 solution, made by mixing 115.65 ml. of 0.2 *M* dibasic sodium phosphate, 184.35 ml. of 0.1 *M* citric acid, and 30 mg. of thymol: 1 g. of Polycarbophil absorbs not less than 53 g. of pH 8.0 solution.

Packaging and storage—Preserve Polycarbophil in tight containers.

CATEGORY—Absorbent (gastrointestinal).

USUAL DOSE—**500 mg.** four times a day.

Polyethylene Glycol 300

Polyethylene Glycol 300 is an addition polymer of ethylene oxide and water, represented by the formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, where the average *n* varies from 5 to 5.75. It has an average molecular weight of not less than 285 and not more than 315.

Description—Polyethylene Glycol 300 occurs as a clear, colorless or practically colorless, viscous liquid, having a slight, characteristic odor. It is slightly hygroscopic.

Solubility—Polyethylene Glycol 300 is miscible with water, with alcohol, with acetone and with other glycols. It is insoluble in ether and in aliphatic hydrocarbons, but is soluble in aromatic hydrocarbons. A 25 percent aqueous solution is free from haze or turbidity.

Specific gravity, page 866—The specific gravity of Polyethylene Glycol 300 is not less than 1.124 and not more than 1.130 at 20°.

pH, page 824—The pH of a solution of Polyethylene Glycol 300 (1 in 20) is between 4.0 and 7.0.

Residue on ignition—Gently heat 10 g. of Polyethylene Glycol 300 in a dish or crucible until the glycol is nearly all dissipated. Cool, add 0.5 ml. of sulfuric acid, and ignite: the weight of the residue does not exceed 10 mg. (0.10 percent as sulfate).

Average molecular weight—Add 49 g. of phthalic anhydride, accurately weighed, to 300 ml. of freshly distilled pyridine contained in an amber-colored, glass-stoppered, 1000-ml. bottle. Shake the bottle vigorously until complete solution is effected, and allow to stand overnight to complete the reaction. A 25.0-ml. portion of this reagent must consume between 95 and 100 ml. of 0.5 *N* sodium hydroxide. Pipet 25.0 ml. of the phthalic anhydride-pyridine reagent into a suitable pressure bottle. Transfer about 1.5 g. of Polyethylene Glycol 300, accurately weighed, into the pressure bottle containing the phthalic anhydride-pyridine reagent. Stopper the bottle, wrap securely in a canvas bag, and immerse it in a water bath, previously heated to between 96° and 100°, to the same depth as the mixture in the bottle. Maintain the temperature of the bath between 96° and 100° for 30 minutes. Remove the bottle from the bath and allow to cool in air to room temperature.

Caution: Do not remove the wrapper from the bottle while hot, or hasten cooling by immersing in cold water!

Add to the bottle 50.0 ml. of 0.5 *N* sodium hydroxide and 5 drops of a pyridine solution of phenolphthalein (1 in 100). Titrate with 0.5 *N* sodium hydroxide to a pink end-point that persists for at least 15 seconds. Concomitantly perform a blank determination with the same quantities of the same reagents and in the same manner and record the number of ml. of 0.5 *N* sodium hydroxide required for the actual titration. Calculate the average molecular weight by multiplying the weight of the sample, in g., by 2000 and divide the result by the difference between the number of ml. of 0.5 *N* sodium hydroxide required for the blank and the number of ml. required for titration of the sample multiplied by the normality of the sodium hydroxide.

Packaging and storage—Preserve Polyethylene Glycol 300 in tight containers.

Category—Solvent; dispersing agent.

Polyethylene Glycol 1540

Polyethylene Glycol 1540 is an addition polymer of ethylene oxide and water, represented by the formula $HOCH_2(CH_2OCH_2)_nCH_2OH$, where the average *n* varies from 28 to 36. It has an average molecular weight of not less than 1296 and not more than 1648.

Description—Polyethylene Glycol 1540 occurs as a white, waxy, plastic material, having a consistency similar to beeswax, and having a slight, characteristic odor.

Solubility—Polyethylene Glycol 1540 is freely soluble in water. It is sparingly soluble in dehydrated alcohol, and is freely soluble in chloroform. It is practically insoluble in ether.

Congealing range, page 794—Polyethylene Glycol 1540 congeals between 42° and 46°.

Completeness of solution, page 794—A solution of 5 g. of Polyethylene Glycol 1540 in water to make 50 ml. is practically clear and colorless.

pH, page 824—The pH of a solution of Polyethylene Glycol 1540 (1 in 20) in water is between 4.0 and 7.0.

Acidity—To 20 ml. of alcohol contained in a flask, add 3 drops of phenolphthalein T.S. and 0.1 *N* sodium hydroxide until a permanent pink color is produced. Disregard the volume of the sodium hydroxide consumed. Now dissolve 5 g. of Polyethylene Glycol 1540 in the alcohol, and if the pink color is discharged, add 0.1 *N* sodium hydroxide until it is restored: not more than 0.2 ml. of 0.1 *N* sodium hydroxide is required (about 0.02 percent as CH_3COOH).

Residue on ignition—Gently heat 2.0 g. of Polyethylene Glycol 1540 in a dish or crucible until the glycol is nearly all dissipated. Cool, add 0.5 ml. of sulfuric acid, and ignite: the weight of the residue does not exceed 2.0 mg. (0.10 percent as the sulfate).

Average molecular weight—Remove a sample of Polyethylene Glycol 1540 from the container, transfer it to a suitable beaker or flask, and immerse it in a water bath maintained at 80°, until the sample has melted completely. Transfer about 30 g. of the melted sample, accurately weighed, to a 100-ml. volumetric flask, and dilute to volume with pyridine. Proceed as directed in the test for *Average molecular weight* under *Polyethylene Glycol 300,* page 562, using 25.0 ml. of the pyridine solution of the sample instead of the weight of polyethylene glycol 300 and making the appropriate correction for the sample dilution in calculating the molecular weight.

Packaging and storage—Preserve Polyethylene Glycol 1540 in well-closed containers.

Category—Vehicle.

Polymyxin B Sulfate Tablets

Polymyxin B Sulfate Tablets have a potency of not less than 90.0 percent and not more than 130.0 percent of the labeled potency. Polymyxin B Sulfate Tablets conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Polymyxin B Sulfate Tablets in well-closed containers.

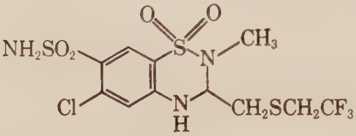
Tablets available—Polymyxin B Sulfate Tablets usually available contain the following equivalents of polymyxin B sulfate: 250,000 and 500,000 USP Units.

Category—Antibacterial (intestinal).

Usual dose of polymyxin b sulfate—Oral, **750,000 USP Units** four times a day.

Polymyxin B Sulfate, Gramicidin and Neomycin Sulfate Ophthalmic Solution, page 475
Polymyxin B Sulfate, Neomycin Sulfate, and Zinc Bacitracin Ointment, page 475

Polythiazide*



6-Chloro-3,4-dihydro-2-methyl-3-[[(2,2,2-trifluoroethyl)thio]-methyl]-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide

$C_{11}H_{13}ClF_3N_3O_4S_3$ Mol. wt. 439.88

Polythiazide, dried in vacuum at 60° for 2 hours, contains not less than 97.0 percent and not more than 101.0 percent of $C_{11}H_{13}ClF_3N_3O_4S_3$.

Description—Polythiazide occurs as a white, crystalline powder having a characteristic odor.

Solubility—Polythiazide is soluble in methanol and in acetone. It is practically insoluble in water and in chloroform.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Polythiazide, previously dried in vacuum at 60° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Polythiazide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Polythiazide in methanol exhibits maxima and minima at the same wavelengths as that of NF Polythiazide Reference Standard, similarly measured.

Loss on drying, page 814—Dry Polythiazide in vacuum at 60° for 2 hours: it loses not more than 1 percent of its weight.

Melting range, page 814—Polythiazide melts with decomposition between 207° and 217°.

Residue on ignition, page 858—Polythiazide yields not more than 0.2 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Polythiazide is 25 parts per million.

Selenium—A *Test Preparation* prepared with 200 mg. of Polythiazide meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Diazotizable substances—

Standard preparation—Weigh accurately 10.0 mg. of NF 4-Amino-6-chloro-1,3-benzene Disulfonamide Reference Standard, and dissolve it in sufficient methanol to make 50.0 ml. Pipet 25.0 ml. of this solution into a 100-ml. volumetric flask, dilute to volume with methanol, and mix.

Test preparation—Dissolve 500.0 mg. of Polythiazide in sufficient methanol to make 100.0 ml.

Procedure—Pipet 2.0 ml. each of the *Standard preparation* and of the *Test preparation* into separate 20-ml. test tubes, and pipet 2.0 ml. of methanol into a third tube to serve as a blank. Place the tubes in a water bath maintained at 70°, evaporate the contents to dryness under a stream of nitrogen, and dissolve each residue in 1.0 ml. of acetonitrile. To each tube add 2.0 ml. of 0.1 *N* hydrochloric acid and 1.0 ml. of sodium nitrite solution (1 in 1000), and allow to stand for 15 minutes with occasional shaking. Add 2.0 ml. of ammonium sulfamate solution (1 in 50), allow to stand for 5 minutes with frequent shaking, then add to each tube 1.0 ml. of freshly prepared *N*-(1-naphthyl)-ethylenediamine dihydrochloride solution (1 in 1000) and 10.0 ml. of sodium acetate T.S., and mix. Transfer each solution to a 50-ml. volumetric flask with the aid of water, dilute to volume with water, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 525 mμ, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance of the solution from the *Test preparation* does not exceed that from the *Standard preparation*, indicating not more than 1 percent of diazotizable substances.

Assay—Transfer about 100 mg. of Polythiazide, previously dried in vacuum at 60° for 2 hours and accurately weighed, to a 250-ml. volumetric flask, add methanol to volume, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Polythiazide Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 268 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{11}H_{13}ClF_3N_3O_4S_3$ in the Polythiazide taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

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* Patented. See notice, page ii.

CATEGORY—Diuretic; antihypertensive.
USUAL DOSE RANGE—**1** to **4 mg.** daily.

Polythiazide Tablets

Polythiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{13}ClF_3N_3O_4S_3$.

Identification—Transfer a portion of finely powdered Polythiazide Tablets, equivalent to 2 mg. of polythiazide, to a 250-ml. flask, add 125 ml. of methanol, and shake for 15 minutes. Dilute to 250 ml. with methanol, mix, and filter, discarding the first 15 ml. of filtrate. Dilute 25 ml. of the subsequent filtrate to 50 ml. with methanol: the ultraviolet absorption spectrum of this solution exhibits maxima and minima at the same wavelengths as that of NF Polythiazide Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Polythiazide Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Polythiazide Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure:

Standard preparation—Transfer about 50 mg. of NF Polythiazide Reference Standard, accurately weighed, to a 50-ml. volumetric flask, add acetone to volume, and mix. Transfer 5.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with acetone, and mix.

Test preparation—Place one tablet in a volumetric flask of such size that 50 ml. is available for each mg. of polythiazide in the tablet, add a few glass beads and an amount of water equal to about 10 percent of the volume of the flask, and shake mechanically for 15 minutes. Add acetone to make about 75 percent of the volume of the flask, shake mechanically for 20 minutes, then dilute to volume with acetone, and mix. Filter, and discard the first 10 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise with acetone, if necessary, to provide a solution containing approximately 20 mcg. of polythiazide per ml.

Procedure—Pipet 5.0 ml. each of the *Standard preparation* and of the *Test preparation* into separate 25-ml. volumetric flasks, and pipet 5.0 ml. of water and 5.0 ml. of acetone into a third flask to serve as a blank. To each flask add 2.5 ml. of 6 *N* hydrochloric acid, and heat in a boiling water bath for 3 minutes. Cool, and add to each flask 15 ml. of water followed by 1 ml. of freshly prepared sodium nitrite solution (1 in 1000). Shake, allow to stand for 3 minutes, then add 1 ml. of ammonium sulfamate solution (1 in 200), shake, and allow to stand again for 3 minutes. To each flask add 1.0 ml. of *N*-(1-naphthyl)-ethylenediamine dihydrochloride solution (1 in 1000), dilute to volume with water, and mix. Immediately and concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 510 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Test preparation* as A_U. Calculate the quantity, in mg., of $C_{11}H_{13}ClF_3N_3O_4S_3$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of polythiazide, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of polythiazide in the *Test preparation,* based upon the labeled quantity per tablet and the extent of dilution; and C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Assay—

Standard preparation—Transfer about 125 mg. of NF Polythiazide Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix.

Assay preparation—Weigh and finely powder not less than 20 Polythiazide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 12.5 mg. of polythiazide, to a 40-ml. glass-stoppered centrifuge tube, add 10.0 ml. of methanol, stopper tightly, and shake mechanically for 30 minutes. Centrifuge at 1500 r.p.m. for 15 minutes, and use the supernatant liquid as directed in the *Procedure.*

Procedure—Apply a 200-μl. portion of the *Standard preparation* to a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, applying the portion as a continuous band 6 cm. in length, 2 cm. from the lower edge of the plate, and starting 2 cm. from the side of the plate. Prepare a duplicate plate for the *Standard preparation*. Similarly, apply a 200-µl. portion of the *Assay preparation* to one plate, and then prepare a duplicate plate for the *Assay preparation*. Allow the spots to dry, and develop the chromatograms in a solvent system consisting of chloroform and methanol (9:1) until the solvent front has moved approximately 15 cm. from the origin. Remove the plates from the developing chamber, and dry for 45 minutes in the air at room temperature. Observe the plates under shortwave ultraviolet light, and outline the absorbent bands occurring at about R_f 0.45 to 0.55. Quantitatively remove the silica gel from these areas from each plate, and transfer to separate 50-ml. conical flasks. For the blanks, transfer an equal amount of polythiazide-free silica gel at the same R_f from each plate to individual 50-ml. conical flasks. Add 25.0 ml. of methanol to each flask, shake for 30 minutes, and filter.

Concomitantly determine the absorbance of each filtrate, in 1-cm. cells, at the maximum at about 268 mµ, with a suitable spectrophotometer, using the respective blank to set the instrument. Calculate the quantity, in mg., of $C_{11}H_{13}ClF_3N_3O_4S_3$ in the portion of Tablets taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, A_U is the average of the absorbances from the *Assay preparation*, and A_S is the average of the absorbances from the *Standard preparation*.

Packaging and storage—Preserve Polythiazide Tablets in tight, light-resistant containers.

Tablets available—Polythiazide Tablets usually available contain the following amounts of polythiazide: 1, 2, and 4 mg.

CATEGORY and DOSE—See Polythiazide.

Posterior Pituitary

Posterior Pituitary is a powder prepared from the clean, dried, posterior lobe of the pituitary of domestic animals used for food by man. Each mg. of Posterior Pituitary possesses an oxytocic activity equivalent to not less than 1 USP Posterior Pituitary Unit.

Description—Posterior Pituitary is a yellowish or grayish, amorphous powder having a characteristic odor.

Histology—It shows numerous pituicytes (neuroglia) with granular contents and branching processes, and spindle-shaped bipolar nerve cells each staining black with silver nitrate solution (1 in 100); scattered fragments of capillaries, containing erythrocytes, their endothelial walls colored pinkish purple and the erythrocytes darker with a mixture of equal parts of dilute Delafield's hematoxylin T.S. (1 in 2) and eosin Y solution (1 in 100); fragments of non-medullated nerve fibers with or without bulbous ends, their axons colored pale purple by the aforementioned hematoxylin and eosin solution; fragments of the pars intermedia including colloid vesicles, scattered irregular-shaped, hyaline fragments of colloid, and rounded to polyhedral chromophile and chromophobe cells, the colloid colored pink, the nuclei of the chromophile and chromophobe cells blue and their cytoplasm pink with the hematoxylin-eosin solution; and irregular flattened fragments of fibrillar tissue, oval to stellate connective tissue cells and granular intercellular substance colored blue to bluish green with a mixture of equal parts of Mallory's stain and phosphotungstic acid solution (1 in 100). Occasional amyloid bodies of ovoid, spheroidal, or crescent shape, and staining a deep purple with water saturated with iodine, occur in some mounts.

Solubility—Posterior Pituitary dissolves incompletely in water.

Loss on drying, page 814—Dry Posterior Pituitary in vacuum at 60° for 4 hours: it loses not more than 5 percent of its weight.

Salmonella, page 862—The test for *Salmonella* in Posterior Pituitary is negative.

Assay—Place about 50 mg., accurately weighed, of Posterior Pituitary in a 250-ml. flask, and add 1 ml. of dilute glacial acetic acid (1 in 400) for each mg. of the powder taken. Insert a small, short-stemmed funnel in the neck of the flask. Heat the flask and contents, with continuous gentle shaking, in a boiling water bath for 5 minutes. Cool the flask under cold running water, and filter. Using the filtrate in place of the Posterior Pituitary Injection to prepare the *Assay preparation*, proceed as directed in the *Assay* under *Posterior Pituitary Injection*, page 567, but in the section, *Calculation*, substitute the following in place of the last three paragraphs: the logarithm of the relative potency of the *Assay preparation* is

$$M' = \{i(T_1 + T_2)/2(T_2 - T_1)\} - \bar{x}.$$

The potency of Posterior Pituitary, in USP Posterior Pituitary Units of oxytocic activity per mg., is R(antilog M'), where $R = v_S/v_U$, in which v_S is the number of

USP Units of oxytocic activity in each ml. of the *Standard preparation*, and v_U is the number of mg. of Posterior Pituitary in each ml. of the *Assay preparation*.

The calculated potency is not less than 0.85 USP Posterior Pituitary Unit of oxytocic activity per mg.

Compute the approximate confidence interval, L (see *Design and Analysis of Biological Assays*, USP XVIII). If L exceeds 0.20, repeat the assay or increase the number of sets of responses until the approximate confidence interval of the combined results is 0.20 or less.

Packaging and storage—Preserve Posterior Pituitary in tight containers, preferably at a temperature not exceeding 30°.

CATEGORY—Posterior pituitary hormones (mixed).

USUAL DOSE—**10 mg.** as snuff three or more times a day as needed.

USUAL DOSE RANGE—**5** to **20 mg.**

Posterior Pituitary Injection

Posterior Pituitary Injection is a sterile solution, in water for injection, of the principles from the posterior lobe of the pituitary of domestic animals used for food by man. Each ml. of Posterior Pituitary Injection possesses USP Posterior Pituitary activity equivalent to 10 Units of oxytocic activity and not less than 5 Units of vasopressin activity.

Description—Posterior Pituitary Injection is a clear or only faintly opalescent liquid. It is colorless, or nearly so, and has a faint, characteristic odor.

pH, page 824—The pH of Posterior Pituitary Injection is between 2.5 and 4.5.

Vasopressin activity—

The animal preparation—About 18 hours prior to the test select a male rat weighing between 275 and 325 g. Subcutaneously inject 10 ml. per kg. of body weight of a solution prepared by dissolving 5 mg. of phenoxybenzamine hydrochloride in 0.1 ml. of alcohol, acidifying with 1 drop of hydrochloric acid, and diluting with saline T.S. to 5 ml.

On the day of the test anesthetize the rat with an anesthetic favorable to the maintenance of a uniform blood pressure. Suitably secure the animal, and cannulate the trachea for artificial respiration. Arrange to record the blood pressure from the carotid artery by means of a suitable, small-bore, mercury manometer using a cannula approximately 1 mm. in external diameter and filled with a 1000-Units-per-ml. solution of sodium heparin in saline T.S. Arrange for intravenous injections through a suitable cannula approximately 1 mm. in external diameter inserted in a femoral or jugular vein. Keep the animal warm during its preparation and during the test.

Preparation of the test dilutions—Prepare a test dilution from the *Standard preparation* in the *Assay*, to contain a known vasopressin activity in the range of 0.1 to 0.4 USP Posterior Pituitary Unit in each ml., the concentration being indicated by the sensitivity of the animal preparation. Dilute 1 ml. of Posterior Pituitary Injection with sufficient saline T.S. to obtain the *Standard/Test preparation* ratio $R = v_S/v_U = 5$ or more, in which v_S is the Unit value of USP Posterior Pituitary vasopressin activity in each ml. of the *Standard preparation*, and v_U is the volume, in ml., of the Injection in each ml. of the *Test preparation*.

Conduct of the test—Determine by trial the three doses of the diluted *Standard preparation* which, when injected intravenously at regular intervals of 12 to 15 minutes, will produce consistent and graded blood-pressure elevations of between 20 and 70 mm. of mercury. Repeat the intermediate dose: the two responses do not differ by more than ±10 percent.

Inject a series of four doses consisting of the intermediate dose of the Standard determined as directed, alternating with the same volume of the unknown test dilution. Measure the change in blood pressure following each of the four doses. The average pressor response to the test dilution of the Injection is equal to or greater than that to the test dilution of the Standard.

Other requirements—Posterior Pituitary Injection meets the requirements under *Injections*, page 810.

Assay—

Standard preparation—Place 50 to 100 mg., accurately weighed, of USP Posterior Pituitary Reference Standard in a 250-ml. flask, and add 0.5 ml. of dilute glacial acetic acid (1 in 400) for each unit of oxytocic activity represented by the weight of Standard taken. Insert a small, short-stemmed funnel in the neck of the flask. Heat the flask and contents, with continuous, gentle shaking, in a boiling water bath for 5 minutes. Cool the flask under cold running water, and filter. Each ml. of the filtrate contains Posterior Pituitary activity equivalent to 2 Units of oxytocic activity and 1.75 Units of vasopressin activity. Place this stock solution in hard-glass ampuls, seal, and heat in flowing steam for 20 minutes on each of three successive days. Store the solution in a refrigerator and use within 6 months.

On the day of the assay, prepare a primary test dilution by adding sufficient saline T.S. to a measured volume of the stock solution so that the resulting *Standard preparation* contains a known oxytocic activity in the range of 0.1 to 0.4 USP Posterior Pituitary Unit in each ml., the concentration being indicated by the *Determination of the sensitivity of the animal preparation.*

Assay preparation—To an accurately measured quantity of Posterior Pituitary Injection add sufficient saline T.S. so that each ml. of the resulting *Assay preparation* is expected to have the same potency as the *Standard preparation.*

The animal—Select a young adult domestic chicken weighing between 1 and 2.5 kg. Anesthetize the chicken deeply enough to prevent voluntary muscular movements, using an anesthetic substance which favors the maintenance of a prolonged anesthesia and a uniform blood pressure. Expose an ischiatic artery by careful dissection, and cannulate it after occluding the afferent branches for a distance of about 2 cm. Arrange to record the blood pressure kymographically, using a manometer of a type with which there is only a small interchange of arterial blood and the anticoagulant fluid of the recording system, but which makes a visible record of arterial pulsation and of changes in blood pressure. Adjust the manometer so that each mm. change in the record corresponds to a change in blood pressure of not more than 2 mm. of mercury. Prepare to inject the test dilutions intravenously by exposing a crural vein or by tying back one of the wings and exposing the brachial vein.

Determination of the sensitivity of the animal preparation—Determine by trial injections the quantity of Standard that elicits a precipitous but evanescent decrease in blood pressure of 20 to 40 mm. of mercury. If necessary at the outset or during the assay, alter the concentration of the *Standard preparation* so that a dose of not less than 0.15 ml. and not more than 0.5 ml. of it elicits a response in the indicated range. If severe tachyphylaxis occurs, as shown by a rapidly decreasing response to successive injections of the Standard, discard the chicken as unsuitable for use in the assay.

Procedure—Inject the selected dose of the *Standard preparation,* and repeat at regular intervals of 3 to 10 minutes thereafter. At the mid-point of the time interval between successive, equal doses of the *Standard preparation,* inject one of two doses of the *Assay preparation* so selected that their geometric mean corresponds approximately to the dose of the *Standard preparation* and the lesser of the two doses is expected to produce a response approximately four-fifths of that of the *Standard preparation.* Inject three or more sets of doses, each set consisting of the low and high levels of the *Assay preparation* and the alternating doses of the *Standard preparation,* randomizing the order of the low and high doses within each set. Keep the dose of the Standard constant as long as the recorded blood pressure decreases are between 20 and 40 mm. of mercury, but if necessary, due to changes in sensitivity of the animal, alter the dose appropriately between sets to keep the responses within this range, starting the next set with the changed dose of the Standard. Whenever the dose of the *Standard preparation* is altered, adjust both doses of the *Assay preparation* so as to maintain the same proportionate relationship between the low and high levels (*i.e.*, a constant log-interval, i) throughout the assay. Measure and record the responses observed to the nearest mm. of mercury.

Calculation—Tabulate, in chronological order, the logarithms of the doses of the *Standard preparation* and of the *Assay preparation* and the respective responses thereto. Average the response to the Standard which immediately precedes and that which immediately follows each response to the *Assay preparation,* and subtract each average from the intervening response. Designate the difference in response as y. Compute similarly the corresponding difference, x, in the respective log-doses and compute the average, $\bar{x}$, of all the values of x. Total the differences, y, to obtain T_1 and T_2 for the low dose and high dose, respectively, of the *Assay preparation.*

The logarithm of the relative potency of the *Assay preparation* is

$$M' = \{i(T_1 + T_2)/2(T_2 - T_1)\} - \bar{x}.$$

The potency of the Injection, in USP Posterior Pituitary Units of oxytocic activity per ml., is R(antilog M'), where $R = v_S/v_U$, in which v_S is the number of USP Units of oxytocic activity in each ml. of the *Standard preparation,* and v_U is the volume, in ml., of the Injection in each ml. of the *Assay preparation*

The calculated oxytocic potency is not less than 8.5 and not more than 12 USP Posterior Pituitary Units per ml.

Compute the approximate confidence interval, L (see *Design and Analysis of Biological Assays*, USP XVIII). If L exceeds 0.20, repeat the assay or increase the number of sets of responses until the approximate confidence interval of the combined results is 0.20 or less.

Packaging and storage—Preserve Posterior Pituitary Injection in single-dose or in multiple-dose containers, preferably of Type I glass. Store in a refrigerator, and do not freeze.

Expiration date—The expiration date is not later than 3 years from date of assay.

Injections available—Posterior Pituitary Injection usually available contains the following: 10 USP Units in 1 ml.; 100 Units in 10 ml.

Category—Posterior pituitary hormones (mixed).

Usual dose—Subcutaneous, 10 USP Units.

Usual dose range—Up to 10 Units.

Sulfurated Potash

Sulfurated potash is a mixture composed chiefly of potassium polysulfides and potassium thiosulfate. It contains not less than 12.8 percent of S (sulfur) in combination as sulfide.

Description—Sulfurated Potash occurs as irregular, liver-brown pieces when freshly made, changing to a greenish yellow. It has an odor of hydrogen sulfide and a bitter, acrid, and alkaline taste, and decomposes upon exposure to air. A solution (1 in 10) is light brown in color and is alkaline to litmus.

Solubility—Sulfurated Potash is freely soluble in water, usually leaving a slight residue. Alcohol dissolves only the sulfides.

Identification—

A: To a 1 in 10 solution of Sulfurated Potash add an excess of acetic acid: hydrogen sulfide is evolved and sulfur is precipitated.

B: Filter the mixture from *Identification test A*, and add to the filtrate an excess of sodium bitartrate T.S.: an abundant, white, crystalline precipitate is formed within 15 minutes.

Assay for sulfides—Transfer 10 to 15 pieces of Sulfurated Potash to a mortar, and reduce to a fine powder. Transfer about 1 g. of the powder, accurately weighed, to a 250-ml. beaker, and dissolve in 50 ml. of water. Filter, if necessary, and wash or dilute to 75 ml. with water. Add, with constant stirring, 50 ml. of cupric sulfate solution (1 in 20), and allow the mixture to stand, with occasional stirring, for 10 minutes. Filter through a retentive filter, and wash the precipitate with 200 ml. of dilute hydrochloric acid (1 in 45), taking care to avoid breaking up the cake. (If the filtrate is not blue in color, discard the sample and start over, using a larger volume of cupric sulfate solution.) Ignite the precipitate in a tared dish at 1000° for 1 hour, cool in a desiccator, and weigh: the weight of the residue, multiplied by 0.4030, represents the weight of S in the sample.

Packaging and storage—Preserve Sulfurated Potash in tight containers. Containers from which it is to be taken for immediate use in compounding prescriptions contain not more than 120 g.

Category—Pharmaceutic aid (source of sulfide).

Lactated Potassic Saline Injection

Lactated Potassic Saline Injection is a sterile solution of KCl (potassium chloride), NaCl (sodium chloride), and $C_3H_5NaO_3$ (sodium lactate) in water for injection. It contains, in each 100 ml., not less than 126 mg. and not more than 147 mg. of potassium (K, equivalent to not less than 240 mg. and not more than 280 mg. of KCl); not less than 262 mg. and not more than 294 mg. of sodium (Na, equivalent to not less than 380 mg. and not more than 420 mg. of NaCl, and not less than 550 mg. and not more than 630 mg. of $C_3H_5NaO_3$); not less than 344 and not more than 388 mg. of chloride ion (Cl, as KCl and NaCl); and not less than 437 mg. and not more than 501 mg. of lactate ion ($C_3H_5O_3$, as $C_3H_5NaO_3$). It contains no bacteriostatic agents.

Note—The potassium and sodium contents of Lactated Potassic Saline Injection are approximately 3.5 and 12 milliequivalents per 100 ml., respectively.

Identification—Lactated Potassic Saline Injection responds to the tests for *Chloride*, page 808, *Lactate*, page 809, *Potassium*, page 809, and *Sodium*, page 810.

pH, page 824—The pH of Lactated Potassic Saline Injection is between 6.5 and 7.5.

Arsenic—A 100-ml. portion of Lactated Potassic Saline Injection, concentrated to 35 ml., meets the requirements of the *Arsenic Test*, page 777 (0.1 part per million As).

Heavy metals, page 806—To 20 ml. of Lactated Potassic Saline Injection add 2 ml. of diluted acetic acid, then add water to make 25 ml.: the heavy metals limit for Lactated Potassic Saline Injection is 0.3 part per million.

Pyrogen—Lactated Potassic Saline Injection meets the requirements of the *Pyrogen Test*, page 851.

Other requirements—Lactated Potassic Saline Injection meets the requirements under *Injections*, page 810.

Potassium content—

Standard solutions—Prepare five standard solutions (*1*, *2*, *3*, *4*, and *5*) each containing about 0.02 percent of a suitable nonionic wetting agent and 101.6 mg. of sodium chloride per liter, and to the solutions add, respectively 0-, 5-, 10-, 15-, and 20-mg. supplements of potassium, in the form of the chloride, per liter, and mix. If necessary, because of changes in the sensitivity of the instrument mentioned below, vary the levels of concentration of the potassium, keeping the ratios between solutions approximately as given.

Standard graph—Set a suitable flame photometer for maximum transmittance at a wavelength of 766 $m\mu$ to 767 $m\mu$. (The exact wavelength setting will vary slightly with the instrument.) Adjust the instrument to zero transmittance with solution *1*. Then adjust the instrument to 100 percent transmittance with solution *5*. Read the percentage transmittance of solutions *2*, *3*, and *4*. Plot the observed transmittance of solutions *2*, *3*, *4*, and *5* as the ordinate and the concentration of potassium as the abscissa on arithmetic coordinate paper.

Procedure—Pipet a volume of Lactated Potassic Saline Injection, equivalent to about 18 mg. of potassium or a quantity corresponding to the concentration of the *Standard solutions*, into a 1000-ml. volumetric flask. Add 0.02 percent of a suitable nonionic wetting agent, dilute to volume, and mix. Adjust the instrument to zero transmittance with solution *1*, and to 100 percent transmittance with solution *5*. Read the percentage transmittance of the test solution, and, by reference to the standard potassium graph, calculate the potassium content of the sample in mg. of potassium per 100 ml.

Sodium content—Proceed as directed under *Potassium content*, with the following modifications: (1) prepare the *Standard solutions* to contain 19.07 mg. of potassium chloride per liter, and substitute sodium for the stated quantities of potassium; (2) prepare the *Standard graph* with the flame photometer set for maximum transmittance at a wavelength of 588 $m\mu$ to 589 $m\mu$; and (3) under *Procedure* read "sodium" for "potassium" throughout.

Chloride content—Pipet 25.0 ml. of Lactated Potassic Saline Injection into a glass-stoppered flask, and add 25 ml. of water. Add 3 ml. of nitric acid, previously diluted with 5 ml. of water, then, while agitating the mixture, slowly add 50.0 ml. of 0.1 *N* silver nitrate. Add 5 ml. of nitrobenzene, shake vigorously for 1 minute, add 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 3.545 mg. of Cl.

Lactate content—Pipet 50.0 ml. of Lactated Potassic Saline Injection into a suitable crucible or dish, evaporate to dryness, and ignite gently until thoroughly charred. Break up the charred mass well with a glass rod, add 25 ml. of water and 50.0 ml. of 0.1 *N* sulfuric acid, and heat on a steam bath for 30 minutes, breaking up any lumps with a glass rod during the heating. Filter, wash with hot water until the last washing is neutral to litmus paper, cool the combined filtrate and washings, add 3 drops of methyl orange T.S., and titrate the excess acid with 0.1 *N* sodium hydroxide. Each ml. of 0.1 *N* sulfuric acid is equivalent to 8.907 mg. of $C_3H_5O_3$.

Packaging and storage—Preserve Lactated Potassic Saline Injection in single-dose containers, preferably of Type I or Type II glass.

Injections available—Lactated Potassic Saline Injection is usually available in the following volumes: 150, 250, 500, and 1000 ml.

CATEGORY—Fluid and electrolyte replenisher.

USUAL DOSE RANGE—Intravenous and subcutaneous, **40 to 80 ml.** per kg. of body weight per day, given slowly over a period of 4 to 12 hours.

Potassium Acetate

CH_3COOK

$C_2H_3KO_2$ Mol. wt. 98.15

Potassium Acetate, dried at 150° for 2 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_2H_3KO_2$.

Description—Potassium Acetate occurs as colorless, monoclinic crystals or as a white, crystalline powder. It has a saline and slightly alkaline taste. Potassium Acetate deliquesces on exposure to moist air.

Solubility—Potassium Acetate is very soluble in water and is freely soluble in alcohol.

Identification—A solution of Potassium Acetate (1 in 10) responds to the tests for *Potassium*, page 809, and for *Acetate*, page 807.

pH, page 824—A solution of Potassium Acetate (1 in 20) has a pH of 7.5 to 8.5.

Arsenic—A solution of 1.25 g. of Potassium Acetate in water meets the requirements of the *Arsenic Test*, page 777 (8 parts per million As).

Heavy metals, page 806—Dissolve 1 g. of Potassium Acetate in 10 ml. of water, add 3.5 ml. of diluted acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Potassium Acetate is 20 parts per million.

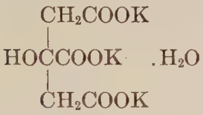
Assay—Dissolve about 200 mg. of Potassium Acetate, previously dried at 150° for 2 hours and accurately weighed, in 25 ml. of glacial acetic acid. Add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 9.815 mg. of $C_2H_3KO_2$.

Packaging and storage—Preserve Potassium Acetate in tight containers

Category—Alkalizer.

Usual dose—**1 g.**

Potassium Citrate



$$\begin{array}{c} CH_2COOK \\ | \\ HOCCOOK \quad .H_2O \\ | \\ CH_2COOK \end{array}$$

Tripotassium Citrate

$C_6H_5K_3O_7 . H_2O$ Mol. wt. 324.42

Potassium Citrate, dried at 180° for 4 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_6H_5K_3O_7$.

Description—Potassium Citrate occurs as transparent crystals, or as a white, granular powder. It is odorless, has a cooling, saline taste, and is deliquescent when exposed to moist air.

Solubility—Potassium Citrate is freely soluble in water. It is almost insoluble in alcohol.

Identification—A solution of Potassium Citrate (1 in 10) responds to the tests for *Potassium*, page 809, and for *Citrate*, page 808.

Alkalinity—A solution of 1 g. of Potassium Citrate in 20 ml. of water is alkaline to litmus, but after the addition of 0.2 ml. of 0.1 *N* sulfuric acid no pink color is produced by the addition of 1 drop of phenolphthalein T.S.

Loss on drying, page 814—Dry Potassium Citrate at 180° for 4 hours: it loses not less than 3 percent and not more than 6 percent of its weight.

Tartrate—To a solution of 1 g. of Potassium Citrate in 1.5 ml of water in a test tube add 1 ml. of acetic acid and scratch the walls of the test tube with a glass rod: no crystalline precipitate is produced.

Heavy metals, page 806—Dissolve 2 g. of Potassium Citrate in 10 ml. of water, add 6 ml. of diluted acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Potassium Citrate is 10 parts per million.

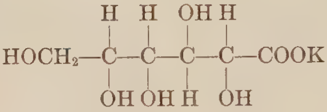
Assay—Dissolve about 200 mg. of Potassium Citrate, previously dried at 180° for 4 hours and accurately weighed, in 25 ml. of glacial acetic acid. Add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 10.21 mg. of $C_6H_5K_3O_7$.

Packaging and storage—Preserve Potassium Citrate in tight containers.

Category—Alkalizer.

Usual dose—**1 g.**

Potassium Gluconate



$$HOCH_2-\underset{OH}{\overset{H}{C}}-\underset{OH}{\overset{H}{C}}-\underset{H}{\overset{OH}{C}}-\underset{OH}{\overset{H}{C}}-COOK$$

$C_6H_{11}KO_7$ Mol. wt. 234.25

Potassium Gluconate contains not less than 97.0 percent and not more than 103.0 percent of $C_6H_{11}KO_7$, calculated on the dried basis.

Description—Potassium Gluconate occurs as a white to yellowish white, crystalline powder or as granules. It is odorless and has a slightly bitter taste. It is stable in air, and its solutions are slightly alkaline to litmus.

Solubility—Potassium Gluconate is freely soluble in water. It is practically insoluble in dehydrated alcohol, in ether, in benzene, and in chloroform.

Identification—Potassium Gluconate responds to the flame test for *Potassium*, page 809.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Potassium Gluconate, previously dried in vacuum at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Potassium Gluconate Reference Standard, similarly measured.

Loss on drying, page 814—Dry Potassium Gluconate in vacuum at 105° for 4 hours: it loses not more than 3 percent of its weight.

Heavy metals, page 806—Dissolve 2 g. of Potassium Gluconate in 10 ml. of water, add 6 ml. of diluted hydrochloric acid, and dilute to 25 ml. with water: the heavy metals limit for Potassium Gluconate is 20 parts per million.

Assay—

Sodium stock solution—Transfer 7.306 g. of sodium chloride, previously dried at 125° for 30 minutes and accurately weighed, to a 500-ml. volumetric flask, add water to volume, and mix. This solution contains 250 meq. (equivalent to 5.76 g.) of Na per 1000 ml.

Potassium stock solution—Transfer 745.5 mg. of potassium chloride, previously dried at 125° for 30 minutes and accurately weighed, to a 1000-ml. volumetric flask, add water to volume, and mix. This solution contains 10 meq. (equivalent to 391 mg.) of K per 1000 ml.

Surfactant solution—Transfer 5.0 g. of a suitable nonionic surfactant to a 250-ml. beaker, add 200 ml. of water, and stir to dissolve. Quantitatively transfer this solution to a 500-ml. volumetric flask, dilute to volume with water, and mix. (*Caution:* To prevent foaming when using this solution, gently run the solution down the sides of the vessel, and use gentle action when mixing.)

Diluted sodium solution—Transfer 50.0 ml. of *Sodium stock solution* and 10.0 ml. of *Surfactant solution* to a 100-ml. volumetric flask, dilute to volume with water, and mix gently to prevent foaming.

Standard preparation—Transfer 5.0 ml. of *Potassium stock solution*, 50.0 ml. of *Sodium stock solution*, and 10.0 ml. of *Surfactant solution* to a 500-ml. volumetric flask, dilute to volume with water, and mix gently to prevent foaming. Each ml. of this solution contains 3.910 mcg. of K.

Assay preparation—Transfer about 120 mg. of Potassium Gluconate, accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix. Filter a portion of the solution through Whatman No. 2V or equivalent filter paper, and transfer 2.0 ml. of the filtrate to a 100-ml. volumetric flask. To the flask add 50 ml. of water, then add 20.0 ml. of *Diluted sodium solution*, dilute to volume with water, and mix gently to prevent foaming.

Procedure—Concomitantly determine the transmittance of the *Standard preparation* and of the *Assay preparation*, at 766 mμ to 767 mμ, with a suitable flame photometer, setting the instrument to zero transmittance with a solution prepared by mixing 50.0 ml. of *Sodium stock solution* and 10.0 ml. of *Surfactant solution* and diluting to 500.0 ml. with water, and adjusting the instrument so that the *Standard preparation* gives a reading near mid-scale. Calculate the weight, in mg., of $C_6H_{11}KO_7$ in the Potassium Gluconate taken by the formula $5 \times 3.91 \times (T_U/T_S) \times (5.990)$, in which T_U is the transmittance of the *Assay preparation*, T_S is the transmittance of the *Standard preparation*, and 5.990 is the ratio of the molecular weight of potassium gluconate to the atomic weight of potassium.

Packaging and storage—Preserve Potassium Gluconate in tight containers.

CATEGORY—Electrolyte replenisher.

USUAL DOSE—The equivalent of 10 meq. of potassium four times daily.

Potassium Gluconate Elixir

Potassium Gluconate Elixir contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{11}KO_7$.

Identification—

A: Potassium Gluconate Elixir responds to the flame test for *Potassium,* page 809.

B: Evaporate 5 ml. of Potassium Gluconate Elixir to dryness on a steam bath: a mineral oil dispersion of the residue exhibits an infrared absorption maximum in the range of 6.2 μ to 6.25 μ (*carboxylic acid salt*).

Assay—

Sodium stock solution, Potassium stock solution, Surfactant solution, and *Diluted sodium solution*—Prepare as directed in the *Assay* under *Potassium Gluconate,* page 572.

Standard preparation—Transfer 4.0 ml. of *Potassium stock solution,* 50.0 ml. of *Sodium stock solution,* and 10.0 ml. of *Surfactant solution* to a 500-ml. volumetric flask, dilute to volume with water, and mix gently to prevent foaming. Each ml. of this solution contains 3.128 mcg. of K.

Assay preparation—Transfer an accurately measured volume of Potassium Gluconate Elixir, equivalent to about 1.87 g. of potassium gluconate, to a 1000-ml. volumetric flask, dilute to volume with water, and mix. Transfer 1.0 ml. of this solution to a 100-ml. volumetric flask, add 20.0 ml. of *Diluted sodium solution,* dilute to volume with water, and mix gently to prevent foaming.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Potassium Gluconate,* page 572. Calculate the weight, in g., of $C_6H_{11}KO_7$ in each ml. of the Elixir taken by the formula $0.1 \times (3.128/V) \times (T_U/T_S) \times 5.990$, in which V is the volume, in ml., of the Elixir taken.

Alcohol content—Determine the alcohol content by the gas-liquid chromatographic procedure, page 773, using acetone as the internal standard. Potassium Gluconate Elixir contains from 4.5 to 5.5 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Potassium Gluconate Elixir in tight, light-resistant containers.

Elixir available—Potassium Gluconate Elixir available usually contains 4.68 g. of potassium gluconate in each 15 ml., equivalent to 20 meq. (782 mg.) of potassium.

CATEGORY and DOSE—See Potassium Gluconate.

Potassium Gluconate Tablets

Potassium Gluconate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{11}KO_7$.

Identification—

A: Triturate a portion of powdered Potassium Gluconate Tablets with a few ml. of water and filter: the filtrate responds to the flame test for *Potassium,* page 809.

B: The infrared spectrum of a mineral oil dispersion, prepared from finely powdered Potassium Gluconate Tablets, exhibits maxima at the same wavelengths as that of NF Potassium Gluconate Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Potassium Gluconate Tablets is 30 minutes.

Weight variation, page 901—Potassium Gluconate Tablets meet the requirements of the weight variation test for tablets.

Assay—

Sodium stock solution, Potassium stock solution, Surfactant solution, Diluted sodium solution, and *Standard preparation*—Prepare as directed in the *Assay* under *Potassium Gluconate,* page 572.

Assay preparation—Weigh and finely powder not less than 20 Potassium Gluconate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 1.2 g. of potassium gluconate, to a 1000-ml. volumetric flask, add water to volume, and mix thoroughly to dissolve. Filter a portion of the solution through Whatman No. 2V or equivalent filter paper, and transfer 2.0 ml. of the filtrate to a 100-ml. volumetric flask. To the flask add 50 ml. of water, then add 20.0 ml. of *Diluted sodium solution,* dilute to volume with water, and mix gently to prevent foaming.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Potassium Gluconate.* Calculate the quantity, in g., of $C_6H_{11}KO_7$ in the portion of Tablets taken by the formula $0.05 \times 3.91 \times$

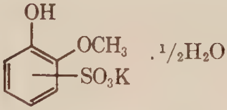
$(T_U/T_S) \times 5.990$.

Packaging and storage—Preserve Potassium Gluconate Tablets in tight containers.

Tablets available—Potassium Gluconate Tablets usually available contain the following amount of potassium gluconate: 1.17 g., equivalent to 5 meq. (195.5 mg.) of potassium.

CATEGORY and DOSE—See Potassium Gluconate.

Potassium Guaiacolsulfonate



Potassium Hydroxymethoxybenzenesulfonate

$C_7H_7KO_5S \cdot {}^1/_2H_2O$ Mol. wt. 251.30

Potassium Guaiacolsulfonate contains not less than 98.0 percent and not more than 102.0 percent of $C_7H_7KO_5S$, calculated on the anhydrous basis.

Description—Potassium Guaiacolsulfonate occurs as white crystals, or as a white, crystalline powder. It has a slight aromatic odor, and a slightly bitter taste. Its water solutions are neutral or alkaline to litmus. It is affected by light.

Solubility—Potassium Guaiacolsulfonate is freely soluble in water. It is practically insoluble in alcohol and in ether.

Identification—

A: To a solution of Potassium Guaiacolsulfonate (1 in 100), add 2 drops of ferric chloride T.S.: a violet-blue color is produced.

B: Ignite a portion of Potassium Guaiacolsulfonate: the ash imparts a violet color to a nonluminous flame.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Potassium Guaiacolsulfonate, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Potassium Guaiacolsulfonate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Potassium Guaiacolsulfonate, prepared as directed in the *Assay*, exhibits maxima and minima at the same wavelengths as that of NF Potassium Guaiacolsulfonate Reference Standard, similarly measured.

Water, page 900—Determine the water content of Potassium Guaiacolsulfonate by the titrimetric method: not less than 3 percent and not more than 6 percent is found.

Selenium—A *Test Preparation* prepared with 200 mg. of Potassium Guaiacolsulfonate meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Sulfate—To 10 ml. of a solution of Potassium Guaiacolsulfonate (1 in 20), add 5 drops of barium chloride T.S., and acidify with hydrochloric acid: no turbidity is produced in 1 minute.

Heavy metals, page 806—Dissolve 1 g. of Potassium Guaiacolsulfonate in 1 ml. of diluted acetic acid and enough water to make 25 ml.: the heavy metals limit for Potassium Guaiacolsulfonate is 20 parts per million.

Assay—Transfer about 250 mg. of Potassium Guaiacolsulfonate, accurately weighed, to a 500-ml. volumetric flask, dissolve in 400 ml. of water, dilute to volume with water, and mix. Dilute 10.0 ml. of this solution to 100.0 ml. with pH 7.0 phosphate buffer, page 783, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Potassium Guaiacolsulfonate Reference Standard similarly prepared, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 279 mμ, with a suitable spectrophotometer, using a mixture of water and pH 7.0 phosphate buffer (1 in 10) as the blank. Calculate the quantity, in mg., of $C_7H_7KO_5S$ in the Potassium Guaiacolsulfonate taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., calculated on the anhydrous basis, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Potassium Guaiacolsulfonate in well-closed, light-resistant containers.

CATEGORY—Expectorant.
USUAL DOSE—**500 mg.**

Potassium Iodide Solution

Potassium Iodide Solution contains, in each 100 ml., not less than 97.0 g. and not more than 103.0 g. of KI.

Potassium Iodide	**1000 g.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Dissolve the salt in 680 ml. of hot purified water; cool to about 25°, and add sufficient purified water to make 1000 ml.; filter, if necessary.

NOTE: If Potassium Iodide Solution is not to be used within a short time, 500 mg. of sodium thiosulfate should be added to each liter.

Description—Potassium Iodide Solution is a clear, colorless, and odorless liquid, with a characteristic, strongly salty taste. It is neutral or alkaline to litmus. Its specific gravity is about 1.70.

Identification—Potassium Iodide Solution responds to the tests for *Potassium,* page 809, and for *Iodide,* page 808.

Assay—Dilute 5 ml of Potassium Iodide Solution, accurately measured, to 100.0 ml., with water. To 10.0 ml. of this dilution in a glass-stoppered flask, add 15 ml. of water, 30 ml. of hydrochloric acid, and 5 ml. of chloroform. Cool to about 10°, and titrate with 0.05 *M* potassium iodate until the purple color of iodine disappears from the chloroform. Add the last portions of the iodate solution dropwise, agitating the mixture vigorously. After the chloroform has been decolorized, allow the mixture to stand for 5 minutes. If the chloroform develops a purple color, titrate further with the iodate solution. Each ml. of 0.05 *M* potassium iodate is equivalent to 16.60 mg. of KI.

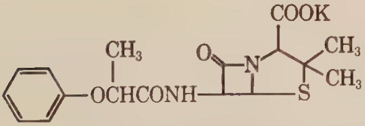
Packaging and storage—Preserve Potassium Iodide Solution in tight, light-resistant containers.

CATEGORY—Iodide supplement; expectorant.

USUAL DOSE—**0.3 ml.**

One usual dose contains 300 mg. of potassium iodide.

Potassium Phenethicillin*



Potassium (1-Phenoxyethyl)penicillin

Potassium 3,3-Dimethyl-7-oxo-6-(2-phenoxypropionamido)-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate

$C_{17}H_{19}KN_2O_5S$ Mol. wt. 402.52

Potassium Phenethicillin occurs as crystalline potassium DL-α-phenoxyethyl penicillin and contains not less than 90.0 percent of $C_{17}H_{19}KN_2O_5S$. It contains not less than 55.0 percent and not more than 75.0 percent of potassium L-α-phenoxyethyl penicillin. Potassium Phenethicillin conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Potassium Phenethicillin in tight containers.

CATEGORY—Antibacterial.

USUAL DOSE—**125** or **250 mg.** three times a day.

USUAL DOSE RANGE—**125** to **500 mg.**

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* Patented. See notice, page ii.

Potassium Phenethicillin for Oral Solution

Potassium Phenethicillin for Oral Solution is a dry mixture of potassium phenethicillin with or without one or more suitable coloring and flavoring agents. It contains potassium phenethicillin equivalent to not less than 85.0 percent of the labeled amount of phenethicillin activity. It may coutain one or more suitable buffers and preservatives. Potassium Phenethicillin for Oral Solution conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Potassium Phenethicillin for Oral Solution in tight containers.

Sizes available—Potassium Phenethicillin for Oral Solution usually available contains the following amounts of phenethicillin activity: 1.5 g. in a 60-ml. container and 3.75 g. in a 150-ml. container.

CATEGORY and DOSE—See Potassium Phenethicillin.

Potassium Phenethicillin Tablets

Potassium Phenethicillin Tablets contain potassium phenethicillin equivalent to not less than 85.0 percent of the labeled amount of phenethicillin activity. Potassium Phenethicillin Tablets conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Potassium Phenethicillin Tablets in tight containers.

Tablets available—Potassium Phenethicillin Tablets usually available contain the following amounts of phenethicillin activity: 125 and 250 mg.

CATEGORY and DOSE—See Potassium Phenethicillin.

Monobasic Potassium Phosphate

Potassium Dihydrogen Phosphate

KH_2PO_4 Mol. wt. 136.09

Monobasic Potassium Phosphate, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 100.5 percent of KH_2PO_4.

Description—Monobasic Potassium Phosphate occurs as colorless crystals or as a white, granular or crystalline powder. It is odorless and is stable in air. The pH of a 1 in 100 solution is about 4.5.

Solubility—Monobasic Potassium Phosphate is freely soluble in water. It is practically insoluble in alcohol.

Identification—A solution of Monobasic Potassium Phosphate (1 in 20) responds to the tests for *Potassium*, page 809, and for *Phosphate*, page 809.

Loss on drying, page 814—Dry Monobasic Potassium Phosphate at 105° for 4 hours: it loses not more than 1 percent of its weight.

Insoluble substances—Dissolve 10 g. of Monobasic Potassium Phosphate in 100 ml. of hot water, filter through a tared filtering crucible, wash the insoluble residue with hot water, and dry at 105° for 2 hours: the residue does not exceed 20 mg. (0.2 percent).

Fluoride—Place 5.0 g. of Monobasic Potassium Phosphate, 25 ml. of water, 50 ml. of perchloric acid, 5 drops of silver nitrate solution (1 in 2), and a few glass beads in a 250-ml. distilling flask connected with a condenser and carrying a thermometer and a capillary tube, both of which must extend into the liquid. Connect a small dropping funnel, filled with water, or a steam generator to the capillary tube. Support the flask on an asbestos mat with a hole which exposes about one-third of the flask to the flame. Distil into a 250-ml. flask until the temperature reaches 135°. Add water from the funnel or introduce steam through the capillary to maintain the temperature between 135° and 140°. Continue the distillation until 225 to 240 ml. has been collected, then dilute to 250.0 ml. with water, and mix.

Transfer 50.0 ml. of this solution to a 100-ml. color-comparison tube, and transfer 50.0 ml. of water to a similar tube to serve as a control. Add to each tube 0.1 ml. of a filtered solution of sodium alizarinsulfonate (1 in 1000) and 1 ml. of freshly prepared hydroxylamine hydrochloride solution (1 in 4000), and mix well. Add, dropwise, and with stirring, 0.05 *N* sodium hydroxide to the tube containing the distillate until its color just matches that of the control, which is faintly pink. Then add to each tube 1.0 ml. of 0.1 *N* hydrochloric acid, and mix well. From a buret, graduated in 0.05-ml., add slowly to the tube containing the distillate enough thorium nitrate solution (1 in 4000) so that, after mixing, the color of the liquid just changes to a faint pink. Note the volume of the solution added, add exactly the same volume to the control, and mix. Now add to the control sodium fluoride T.S. (10 mcg. F per ml.) from a buret to make the colors of the two tubes match after dilution to the same volume. Mix well, and allow all air bubbles to escape before making the final color comparison. Check the end-point by adding 1 or 2 drops of sodium fluoride T.S. to the control. A distinct change in color should take place. Note the volume of sodium fluoride added: the volume of sodium fluoride T.S. required for the control solution does not exceed 1.0 ml. (10 parts per million).

Arsenic—A solution of 3.3 g. of Monobasic Potassium Phosphate in water meets the requirements of the *Arsenic Test*, page 777 (3 parts per million As).

Heavy metals, page 806—Dissolve 2 g. of Monobasic Potassium Phosphate in 25 ml. of water: the heavy metals limit is 20 parts per million.

Lead—A solution of 1 g. of Monobasic Potassium Phosphate in 20 ml. of water contains not more than 5 mcg. of lead (corresponding to not more than 5 parts per million of Pb) when tested according to the *Lead Limit Test*, page 813.

Assay—Transfer about 5 g. of Monobasic Potassium Phosphate, previously dried at 105° for 4 hours and accurately weighed, to a 250-ml. beaker, add 100 ml. of water and 5.0 ml. of 1 *N* hydrochloric acid, and stir until the sample is completely dissolved. Place the electrodes of a suitable pH meter in the solution, and slowly titrate the excess acid, stirring constantly, with 1 *N* sodium hydroxide to the inflection point occurring at about pH 4. Record the buret reading, and calculate the volume (A), if any, of 1 *N* hydrochloric acid consumed by the sample. Continue the titration with 1 *N* sodium hydroxide until the inflection point occurring at about pH 8.8 is reached, record the buret reading, and calculate the volume (B) of 1 *N* sodium hydroxide required in the titration between the two inflection points (pH 4 and pH 8.8). Each ml. of the volume $B - A$ of 1 *N* sodium hydroxide is equivalent to 136.1 mg. of KH_2PO_4.

Packaging and storage—Preserve Monobasic Potassium Phosphate in tight containers.

Category—Buffering agent.

Potassium Sodium Tartrate

$$\begin{array}{l}\text{HOCHCOOK}\\ \quad|\\ \text{HOCHCOONa}\end{array}.4H_2O$$

$C_4H_4KNaO_6.4H_2O$ Mol. wt. 282.23

Potassium Sodium Tartrate contains not less than 99.0 percent and not more than 100.5 percent of $C_4H_4KNaO_6$, calculated on the anhydrous basis.

Description—Potassium Sodium Tartrate occurs as colorless crystals, or as a white, crystalline powder, having a cooling, saline taste. As it effloresces slightly in warm, dry air, the crystals are often coated with a white powder.

Solubility—Potassium Sodium Tartrate is freely soluble in water. It is practically insoluble in alcohol.

Identification—

A: Ignite Potassium Sodium Tartrate: it emits the odor of burning sugar and leaves a residue which is alkaline to litmus and which effervesces with acids.

B: To 10 ml. of a solution of Potassium Sodium Tartrate (1 in 20) add 10 ml. of acetic acid: a white, crystalline precipitate is formed within 15 minutes.

C: A solution of Potassium Sodium Tartrate (1 in 10) responds to the tests for *Tartrate*, page 810.

Alkalinity—A solution of 1 g. of Potassium Sodium Tartrate in 20 ml. of water is alkaline to litmus, but after the addition of

0.2 ml. of 0.1 N sulfuric acid no pink color is produced by the addition of 1 drop of phenolphthalein T.S.

Water, page 900—Determine the water content of Potassium Sodium Tartrate by the titrimetric method (*Residual Titration* procedure): not less than 21 percent and not more than 27 percent is found.

Ammonia—Heat a 5-ml. portion of a solution of Potassium Sodium Tartrate (1 in 10) with 5 ml. of sodium hydroxide T.S.: the odor of ammonia is not noticeable.

Heavy metals, page 806—Dissolve 2 g. of Potassium Sodium Tartrate in 25 ml. of water: the heavy metals limit for Potassium Sodium Tartrate is 10 parts per million.

Assay—Transfer about 250 mg. of Potassium Sodium Tartrate, finely powdered and accurately weighed, to a 250-ml. beaker, add 150 ml. of glacial acetic acid, and boil gently until solution is effected. Cool, add 3 drops of crystal violet T.S., and titrate with 0.1 N perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N perchloric acid is equivalent to 10.51 mg. of $C_4H_4KNaO_6$.

Packaging and storage—Preserve Potassium Sodium Tartrate in tight containers.

CATEGORY—Cathartic.
USUAL DOSE—**10 g.**

Potassium Sorbate

$CH_3—CH{=}CH—CH{=}CH—COOK$

2,4-Hexadienoic Acid, Potassium Salt

$C_6H_7KO_2$ Mol. wt. 150.22

Potassium Sorbate contains not less than 98.0 percent and not more than 101.0 percent of $C_6H_7KO_2$, calculated on the dried basis.

Description—Potassium Sorbate occurs as white crystals or as a powder, having a characteristic odor. It melts at about 270° with decomposition.

Solubility—Potassium Sorbate is soluble in alcohol and freely soluble in water.

Identification—

A: Dissolve 1 g. of Potassium Sorbate in 10 ml. of water: the solution responds to the tests for *Potassium*, page 809.

B: Dissolve 200 mg. of Potassium Sorbate in 2 ml. of water, and add a few drops of bromine T.S.: the color is discharged.

Acidity or alkalinity—Dissolve 1.1 g. of Potassium Sorbate in 20 ml. of water, and add 3 drops of phenolphthalein T.S. If the solution is colorless, titrate with 0.1 N sodium hydroxide to a pink color that persists for 15 seconds: not more than 1.1 ml. is required. If the solution is pink in color, titrate with 0.1 N hydrochloric acid: not more than 0.8 ml. is required to discharge the pink color.

Loss on drying—Dry Potassium Sorbate at 105° for 3 hours: it loses not more than 1 percent of its weight.

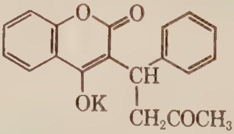
Heavy metals, *Method II*, page 806—The heavy metals limit for Potassium Sorbate is 10 parts per million.

Assay—Dissolve about 300 mg. of Potassium Sorbate, accurately weighed, in 40 ml. of glacial acetic acid, warming if necessary to effect solution. Cool to room temperature, add 1 drop of crystal violet T.S., and titrate with 0.1 N perchloric acid in glacial acetic acid to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 N perchloric acid is equivalent to 15.02 mg. of $C_6H_7KO_2$.

Packaging and storage—Preserve Potassium Sorbate in tight containers.

CATEGORY—Preservative (antimicrobial).

Potassium Warfarin



3-(α-Acetonylbenzyl)-4-hydroxycoumarin Potassium Salt

$C_{19}H_{15}KO_4$ Mol. wt. 346.43

Potassium Warfarin contains not less than 98.0 percent and not more than 102.0 percent of $C_{19}H_{15}KO_4$, calculated on the dried basis.

Description—Potassium Warfarin occurs as a white, odorless, crystalline powder, having a slightly bitter taste. It is discolored by light.

Solubility—Potassium Warfarin is very soluble in water, is freely soluble in alcohol, and is very slightly soluble in chloroform and in ether.

Identification—

A: Dissolve about 100 mg. of Potassium Warfarin in 25 ml. of water, and add hydrochloric acid dropwise to produce a pH of less than 3. Filter the mixture, wash the precipitate with four 5-ml. portions of water, and dry at 105° for 1 hour: the warfarin so obtained melts within a range of 4° between 157° and 167°, page 814.

B: The filtrate obtained in *Identification test A* responds to the tests for *Potassium,* page 809.

Ultraviolet absorption, page 866—The solution of Potassium Warfarin, prepared as directed under *Assay preparation* in the *Assay,* exhibits absorbance maxima and minima at the same wavelengths as that of the *Standard preparation,* prepared as directed in the *Assay,* similarly measured.

pH, page 824—The pH of a solution of Potassium Warfarin (1 in 100) is between 7.2 and 8.3.

Loss on drying, page 814—Dry Potassium Warfarin at 105° to constant weight: it loses not more than 10 percent of its weight.

Heavy metals, page 806—Dissolve 1 g. of Potassium Warfarin in 46 ml. of water, add 4 ml. of diluted acetic acid, stir until the precipitate agglomerates, filter, and use 25 ml. of the filtrate: the heavy metals limit for Potassium Warfarin is 10 parts per million.

Color in alkaline solution—Dissolve 1 g. of Potassium Warfarin, accurately weighed, in sufficient potassium hydroxide solution (1 in 20) to make 10.0 ml., and within 15 minutes determine the absorbance of the solution in a 1-cm. cell at 385 mμ, with a suitable spectrophotometer, using potassium hydroxide solution (1 in 20) as the blank: the absorbance does not exceed 0.20.

Potassium content—Weigh accurately about 400 mg. of Potassium Warfarin, in a tared silica crucible. Ignite until thoroughly charred, cool, then moisten with 0.5 ml. of sulfuric acid, and ignite cautiously until the carbon is consumed and a white residue remains. Heat to constant weight at about 700°, cool, and weigh the residue as potassium sulfate. Each mg. of potassium sulfate is equivalent to 0.4488 mg. of K. Potassium Warfarin contains not less than 10.9 percent and not more than 11.5 percent of K calculated on the dried basis.

Assay—

Standard preparation—Transfer about 100 mg. of USP Warfarin Reference Standard, previously dried in vacuum over phosphorous pentoxide for 4 hours and accurately weighed, to a 100-ml. volumetric flask, dissolve in 10 ml. of 0.1 *N* sodium hydroxide, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a 1000-ml. volumetric flask, dilute to volume with 0.01 *N* sodium hydroxide, and mix.

Assay preparation—Transfer about 110 mg. of Potassium Warfarin, accurately weighed, to a 100-ml. volumetric flask, add 0.01 *N* sodium hydroxide to volume, and mix. Transfer 10.0 ml. of this solution to a 1000-ml. volumetric flask, dilute to volume with 0.01 *N* sodium hydroxide, and mix.

Procedure—Concomitantly determine the absorbance of the *Standard preparation* and of the *Assay preparation* in 1-cm. cells, at the maximum at about 308 mμ, with a suitable spectrophotometer, using 0.01 *N* sodium hydroxide as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{19}H_{15}KO_4$ in the Potassium Warfarin taken by the formula $10C \times 1.124 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Warfarin Reference Standard in the *Standard preparation,* and 1.124 is the ratio of the molecular weight of potassium warfarin to warfarin.

Packaging and Storage—Preserve Potassium Warfarin in well-closed, light-resistant containers.

CATEGORY—Anticoagulant.

USUAL DOSE RANGE—Initial, **25** to **50 mg.,** then **2.5** to **10 mg.** daily in accordance with prothrombin time determinations.

Potassium Warfarin Tablets

Potassium Warfarin Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{19}H_{15}KO_4$.

Identification—

A: Dissolve a quantity of finely powdered Potassium Warfarin Tablets, equivalent to about 100 mg. of potassium warfarin, in 25 ml. of water, and filter if necessary: A 5-ml. portion of the filtrate responds to the tests for *Potassium*, page 809.

B: Triturate a quantity of finely powdered Potassium Warfarin Tablets, equivalent to about 200 mg. of potassium warfarin, with 50 ml. of water, centrifuge, and filter the supernatant liquid. Extract the filtrate with 50 ml. of ether, transfer the aqueous layer to a second separator, and discard the ether. To the separator add hydrochloric acid dropwise to produce a pH of less than 3, and then extract with 50 ml. of chloroform. Transfer the chloroform extract to another separator, extract with 50 ml. of 0.1 *N* sodium hydroxide, and discard the chloroform. Transfer the aqueous layer to a beaker, and adjust to a pH of 3 with hydrochloric acid. Filter, and wash the precipitate with four 5-ml. portions of water. If the precipitate is not white, dissolve it in a minimum volume of 0.1 *N* sodium hydroxide, then dilute with water to about 50 ml., and repeat the foregoing procedure, beginning with "Extract the filtrate with 50 ml. of ether . . . ." Dry the precipitate at 105° for 1 hour: the warfarin so obtained melts within a range of 4° between 157° and 167°, page 814.

C: The ultraviolet absorption spectrum of the solution of warfarin, prepared from Potassium Warfarin Tablets as directed in the *Assay*, exhibits maxima and minima at the same wavelengths as that of the solution of USP Warfarin Reference Standard, prepared as directed in the *Assay*, similarly measured.

D: Dissolve 1 g. of powdered Potassium Warfarin Tablets in 20 ml. of water, and filter. Acidify the filtrate with hydrochloric acid and filter: this solution does not impart a pronounced yellow color to a nonluminous flame when tested on a platinum wire (*absence of sodium*).

Disintegration, page 878—The disintegration time limit for Potassium Warfarin Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Potassium Warfarin Tablets meet the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Potassium Warfarin Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg. of potassium warfarin, to a 250-ml. volumetric flask, add 50 ml. of 0.01 *N* sodium hydroxide, and shake for about 15 minutes. Dilute to volume with 0.01 *N* sodium hydroxide, mix, and filter, discarding the first 20 ml. of filtrate. Transfer 10.0 ml. of the subsequent filtrate to a 125-ml. separator, add 2 ml. of water, and then add hydrochloric acid dropwise to produce a pH of less than 3. Extract with one 25-ml. portion and two 15-ml. portions of chloroform, filtering each extract through a pledget of glass wool into a 100-ml. volumetric flask. Rinse the pledget with a few ml. of chloroform, collecting the rinsings in the flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of USP Warfarin Reference Standard, in chloroform at a concentration of about 15 mcg. per ml., in 1-cm. cells, at the maximum at about 307 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{19}H_{15}KO_4$ in the portion of Tablets taken by the formula $2.5C \times 1.124 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the USP Warfarin Reference Standard solution, 1.124 is the ratio of the molecular weight of potassium warfarin to warfarin, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Potassium Warfarin Tablets in tight, light-resistant containers.

Tablets available—Potassium Warfarin Tablets usually available contain the following amounts of potassium warfarin: 5 and 25 mg.

CATEGORY and DOSE—See Potassium Warfarin.

Povidone

Poly[1-(2-oxo-1-pyrrolidinyl)ethylene]

Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidone groups, the degree of polymerization of which results in polymers of various molecular weights. It is produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000. The viscosity of solutions containing 10 percent or less of Povidone is essentially the same as that of water; solutions more concentrated than 10 percent become more viscous, depending upon the concentration and the molecular weight of the polymer used. Povidone contains not less than 12.0 percent and not more than 13.0 percent of nitrogen, calculated on the dried basis.

Description—Povidone occurs as a white to creamy white, odorless powder. It is hygroscopic.

Solubility—Povidone is soluble in water, in alcohol, and in chloroform. It is insoluble in ether.

Identification—

A: To 10 ml. of a solution of Povidone (1 in 50) add 20 ml. of 1 *N* hydrochloric acid and 5 ml. of potassium dichromate T.S.: an orange-yellow precipitate is produced.

B: Dissolve 75 mg. of cobalt nitrate and 300 mg. of ammonium thiocyanate in 2 ml. of water. To this solution add 5 ml. of Povidone solution (1 in 50), then make the resulting solution acid by the addition of hydrochloric acid T.S.: a pale blue precipitate forms.

C: To 5 ml. of Povidone solution (1 in 200) add a few drops of iodine T.S.: a deep red color is produced.

pH, page 824—The pH of a 1 in 20 solution of Povidone is between 3.0 and 7.0.

Loss on drying, page 814—Dry Povidone to constant weight at 105°: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Povidone yields not more than 0.1 percent of residue on ignition.

Arsenic—A *Test Preparation* prepared with 6.67 g. of Povidone as directed for organic compounds meets the requirements of the *Arsenic Test,* page 777 (1.5 parts per million As).

Lead—Dissolve 1.0 g. of Povidone in 25 ml. of water: this solution contains not more than 10 mcg. of lead (corresponding to not more than 10 parts per million of Pb) when tested according to the *Lead Limit Test,* page 813.

Aldehydes—Transfer 10.0 g. of Povidone to a round-bottom flask containing 180 ml. of dilute sulfuric acid (1 in 4), attach a suitable water-cooled condenser, and reflux for 45 minutes. Re-assemble the apparatus, and distil until about 100 ml. of distillate has been collected, receiving the distillate in a flask, placed in an ice-bath, containing 20 ml. of 1 *N* hydroxylamine hydrochloride previously adjusted to pH 3.1. Add 3 drops of bromophenol blue T.S. to the distillate solution, and titrate with 0.1 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction. Not more than 11.5 ml. of 0.1 *N* sodium hydroxide is required, corresponding to not more than 0.5 percent aldehyde, calculated as acetaldehyde.

Vinylpyrrolidone—Dissolve 4.0 g. of Povidone in 30 ml. of water, add 500 mg. of sodium acetate, and titrate with 0.1 *N* iodine until the color of iodine no longer fades. Add a further 3.0 ml. of 0.1 *N* iodine, allow to stand for 10 minutes, and titrate the excess iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Perform a blank determination (see *Residual Titrations,* page 883): not more than 3.6 ml. of 0.1 *N* iodine is consumed, corresponding to not more than 1 percent of vinylpyrrolidone.

Nitrogen—Determine the nitrogen content as directed under *Nitrogen Determination, Method I,* page 821, using about 1 g. of Povidone, accurately weighed.

Packaging and storage—Preserve Povidone in tight containers.

CATEGORY—Dispersing and suspending agent.

Povidone-Iodine*

Poly[1-(2-oxo-1-pyrrolidinyl)ethylene] Iodine Complex

Povidone-Iodine is a complex of iodine with povidone. Dried at 105° to constant weight, it contains not less than 9.0 percent and not more than 12.0 percent of available I (iodine).

Description—Povidone-Iodine occurs as a yellowish brown, amorphous powder, having a slight, characteristic odor. Its aqueous solution is acid to litmus.

Solubility—Povidone-Iodine is soluble in water and in alcohol. It is practically insoluble in chloroform, in carbon tetrachloride, in ether, in solvent hexane, and in acetone.

Identification—

A: The infrared absorption spectrum of a 1 in 200 potassium bromide dispersion of Povidone-Iodine, previously dried to constant weight at 105°, exhibits maxima at about 6 μ, 7 μ, and 7.7 μ.

B: Add 1 drop of a solution of Povidone-Iodine (1 in 10) to a mixture of 1 ml. of starch T.S. and 9 ml. of water: a deep blue color is produced.

C: Spread 1 ml. of a solution of

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* Patented. See notice, page ii.

Povidone-Iodine (1 in 10) over an area of approximately 20 × 20 cm. on a glass plate, and allow to air-dry overnight at room temperature in an atmosphere of low humidity: a brown, dry, nonsmearing film is formed. The film dissolves readily in water.

Loss on drying, page 814—Dry Povidone-Iodine at 105° to constant weight: it loses not more than 8 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 2 g. of Povidone-Iodine is negligible.

Arsenic—A *Test Preparation* prepared with 6.67 g. of Povidone-Iodine, as directed for organic compounds, meets the requirements of the *Arsenic Test*, page 777 (1.5 parts per million As).

Heavy metals, *Method II*, page 806—The heavy metals limit for Povidone-Iodine is 20 parts per million.

Nitrogen, page 821—Povidone-Iodine, dried at 105° to constant weight, contains not less than 9.5 percent and not more than 11.5 percent of N.

Iodide ion—*Determination of total iodine*—Dissolve about 500 mg. of Povidone-Iodine, accurately weighed, in 100 ml. of water in a 250-ml. conical flask. Add sufficient sodium bisulfite T.S. until the color of iodine has completely disappeared. Add 25.0 ml. of 0.1 *N* silver nitrate and 10 ml. of nitric acid, and mix. Titrate the excess of silver nitrate with 0.1 *N* ammonium thiocyanate, using ferric ammonium sulfate T.S. as indicator. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* silver nitrate is equivalent to 12.69 mg. of I. From the percent of total iodine, subtract the percent of available iodine (see *Assay*) to obtain the percent of iodide ion. The iodide ion content of Povidone-Iodine does not exceed 6.6 percent, calculated on the dried basis.

Assay for available iodine—Place about 500 mg. of Povidone-Iodine, previously dried at 105° to constant weight and accurately weighed, in a 100-ml. beaker, and dissolve it completely in 30 ml. of water. Add 1 ml. of dilute hydrochloric acid (1 in 10), and titrate immediately with 0.02 *N* sodium thiosulfate, adding 3 ml. of starch T.S. as the end-point is neared. Perform a blank determination, and make any necessary correction. Each ml. of 0.02 *N* sodium thiosulfate is equivalent to 2.538 mg. of I.

Packaging and storage—Preserve Povidone-Iodine in tight containers.

CATEGORY—Local anti-infective.

APPLICATION—Topically in various dosage forms which contain available iodine in the range of 0.5 to 3 percent.

Povidone-Iodine Aerosol

Povidone-Iodine Aerosol is a solution of povidone-iodine under nitrogen in a pressurized container. It contains not less than 85.0 percent and not more than 120.0 percent of the labeled amount of I (iodine).

Description and other tests—Spray Povidone-Iodine Aerosol into a beaker or flask until about 50 ml. has been collected, and allow to stand for 5 minutes to allow the entrapped propellant to escape: the solution so obtained conforms to the *Description* and meets the requirements of the tests for *Identification* and *pH*, under *Povidone-Iodine Solution*, page 582.

Other requirements—Povidone-Iodine Aerosol meets the requirements for *Leak Testing* and *Pressure Testing* under *Aerosols*, page 770.

Assay—Transfer to a 100-ml. beaker an accurately measured volume of the solution obtained under *Description and other tests*, equivalent to about 50 mg. of iodine, and continue as directed in the *Assay* under *Povidone-Iodine Solution*, page 582, beginning with " . . . and add water to a total volume of at least 30 ml."

Packaging and storage—Preserve Povidone-Iodine Aerosol in pressurized containers, and avoid prolonged storage at temperature above 120°.

Aerosol available—Povidone-Iodine Aerosol is usually available in the following concentration: 5.0 percent of povidone-iodine, equivalent to 0.5 percent of available iodine.

CATEGORY and APPLICATION—See Povidone-Iodine.

Povidone-Iodine Solution

Povidone-Iodine Solution contains not less than 85.0 percent and not more than 120.0 percent of the labeled amount of I (iodine). It may contain a small amount of alcohol.

Description—Povidone-Iodine Solution is a transparent liquid, having a reddish brown color.

Identification—

A: Dry about 5 g. of Povidone-Iodine Solution in an evaporating dish, in vacuum at 60° until the residue forms a glassy, brittle mass, and finely powder the residue. The infrared absorption spectrum of a potassium bromide dispersion of the powder (1 in 200) exhibits maxima at about 6 μ, 7 μ, and 7.7 μ.

B: Add 1 ml. of a dilution of Povidone-Iodine Solution, containing about 0.05 percent of iodine, to a mixture of 1 ml. of starch T.S. and 9 ml. of water: a deep blue color is produced.

C: Pipet 10.0 ml. of Povidone-Iodine Solution into a 50-ml. conical flask, avoiding contact with the neck of the flask. Cover the mouth of the flask with a small disk of filter paper, and wet it with one drop of starch T.S.: no blue color appears within 60 seconds.

pH, page 824—The pH of Povidone-Iodine Solution is not more than 6.0.

Assay—Transfer to a 100-ml. beaker an accurately measured volume of Povidone-Iodine Solution, equivalent to about 50 mg. of iodine, and add water to a total volume of at least 30 ml. Add 1 ml. of dilute hydrochloric acid (1 in 10), and titrate with 0.02 *N* sodium thiosulfate, adding 3 ml. of starch T.S. as the end-point is neared. Perform a blank determination, and make any necessary correction. Each ml. of 0.02 *N* sodium thiosulfate is equivalent to 2.538 mg. of I.

Alcohol content, page 772—If alcohol is present in Povidone-Iodine Solution, it contains not less than 90 percent and not more than 110 percent (v/v) of the labeled amount of C_2H_5OH.

Packaging and storage—Preserve Povidone-Iodine Solution in tight containers.

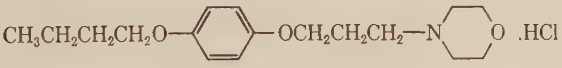
Labeling—If alcohol is present in Povidone-Iodine Solution, the amount, in percent by volume, must be declared on the label.

Solutions available—Povidone-Iodine Solution is usually available in the following concentrations; 5, 7.5, 10, and 30 percent of povidone-iodine, equivalent to 0.5, 0.75, 1, and 3 percent of available iodine.

CATEGORY—See Povidone-Iodine.

Powdered Rauwolfia Serpentina, page 620

Pramoxine Hydrochloride[*]



4-[3-(*p*-Butoxyphenoxy)propyl]morpholine Hydrochloride

$C_{17}H_{27}NO_3.HCl$ Mol. wt. 329.87

Pramoxine Hydrochloride, dried at 105° for 1 hour, contains not less than 98.0 percent and not more than 100.5 percent of $C_{17}H_{27}NO_3.HCl$.

Description—Pramoxine Hydrochloride occurs as a white to nearly white, crystalline powder, having a numbing taste. It may have a slight aromatic odor. The pH of a 1 in 100 solution is about 4.5.

Solubility—Pramoxine Hydrochloride is soluble in chloroform. It is freely soluble in alcohol and in water. It is very slightly soluble in ether.

Identification—

A: Pramoxine Hydrochloride responds to the tests for *Chloride*, page 808.

B: To about 5 mg. of Pramoxine Hydrochloride add 1 drop of nitric acid. To the yellow solution cautiously add 5 drops of stronger ammonia water: a red-brown precipitate forms.

Melting range, *Class Ia*, page 814—Pramoxine Hydrochloride melts between 170° and 174°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Pramoxine Hydrochloride, previously dried at 105° for 1 hour, exhibits maxima only at the same wavelengths as that of NF Pramoxine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Pramoxine Hydrochloride in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Pramoxine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance occurring at about 286 mμ, do not differ by more than 3 percent.

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[*] Patented. See notice, page ii.

Loss on drying, page 814—Dry Pramoxine Hydrochloride at 105° for 1 hour: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Pramoxine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 500 mg. of Pramoxine Hydrochloride, previously dried at 105° for 1 hour and accurately weighed, to a separator, add 20 ml. of 1 *N* hydrochloric acid, dissolve the sample, and mix. Extract the solution with one 35-ml. and three 15-ml. portions of chloroform, collecting the extracts in a 250-ml. conical flask, and evaporate the combined extracts to dryness with the aid of gentle heat and an air stream. Dissolve the residue in 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., add 4 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 32.99 mg. of $C_{17}H_{27}NO_3.HCl$.

Packaging and storage—Preserve Pramoxine Hydrochloride in tight containers.

CATEGORY—Local anesthetic.

APPLICATION—Topically as a 1 percent cream or jelly every 3 to 4 hours.

Pramoxine Hydrochloride Cream

Pramoxine Hydrochloride Cream is pramoxine hydrochloride in a suitable water-miscible base. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{27}NO_3.HCl$.

Identification—Dissolve a quantity of Pramoxine Hydrochloride Cream, equivalent to about 50 mg. of pramoxine hydrochloride, in a mixture of 25 ml. of methanol and 75 ml. of ether, and extract with three 25-ml. portions of a mixture of equal volumes of diluted hydrochloric acid and water. Discard the methanol-ether solution, make the combined extracts alkaline with 25 ml. of sodium hydroxide solution (1 in 5), and then extract the pramoxine base with 50 ml. of chloroform. Evaporate the clear chloroform extract to dryness with the aid of a current of air: a portion of the residue so obtained responds to *Identification test B* and to the test for *Ultraviolet absorption* under *Pramoxine Hydrochloride,* page 583.

Weight variation—Pramoxine Hydrochloride Cream meets the requirements of the weight variation test for creams.

Assay—Weigh accurately into a separator a quantity of Pramoxine Hydrochloride Cream, equivalent to about 50 mg. of pramoxine hydrochloride. Add a mixture of 25 ml. of methanol and 75 ml. of ether, swirl the separator to dissolve the base, and extract with three 25-ml. portions of a mixture of equal volumes of diluted hydrochloric acid and water. Discard the methanol-ether solution, make the combined extracts alkaline with 25 ml. of sodium hydroxide solution (1 in 5), and then extract the pramoxine base with three 25-ml. portions of chloroform. Wash the combined chloroform solution with two 50-ml. portions of water, filter the chloroform solution through filter paper previously moistened with chloroform, and evaporate to dryness on a steam bath, with the aid of a current of air. Dissolve the residue in 50 ml. of glacial acetic acid, warming slightly to effect solution, cool, add 1 drop of crystal violet T.S., and titrate with 0.01 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* perchloric acid is equivalent to 3.299 mg. of $C_{17}H_{27}NO_3.HCl$.

Packaging and storage—Preserve Pramoxine Hydrochloride Cream in tight containers, preferably collapsible tubes.

Cream available—Pramoxine Hydrochloride Cream usually available contains 1 percent of pramoxine hydrochloride.

CATEGORY and APPLICATION—See Pramoxine Hydrochloride.

Pramoxine Hydrochloride Jelly

Pramoxine Hydrochloride Jelly contains not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{17}H_{27}NO_3.HCl$.

Identification—Place an amount of Pramoxine Hydrochloride Jelly, equivalent to about 5 mg. of pramoxine hydrochloride, in a glass-stoppered conical flask, add 25 ml. of chloroform, and shake for 15 minutes. Filter into a small porcelain evaporating dish, and evaporate on a steam bath in a current of air. Add 1 drop of nitric acid to the residue, and to the resulting yellow solution cautiously add 5 drops of stronger ammonia water: a red-brown precipitate forms.

Assay—

Standard preparation—Prepare a solution in 0.5 *N* sulfuric acid containing, in each ml., 150 mcg. of NF Pramoxine Hydrochloride Reference Standard, calculated on the dried basis, and accurately weighed.

Assay preparation—(If emulsions form, 2 to 5 ml. of alcohol may be added to separate the phases.) Transfer an accurately weighed amount of Pramoxine Hydrochloride Jelly, equivalent to about 15 mg. of pramoxine hydrochloride, to a small beaker and dissolve the jelly in 0.1 *N* sulfuric acid, using four 5-ml. portions, warming each portion on a steam bath, and transferring to a 125-ml. separator. To the cooled solution in the separator add 20 ml. of ether, shake carefully, and continue as directed for the *Assay preparation* under *Salts of Organic Nitrogenous Bases*, page 865, beginning with "... and filter the acid phase into a second 125-ml. separator," except combine the final 0.5 *N* sulfuric acid extracts in a 100-ml. volumetric flask, dilute with the acid to volume, and mix.

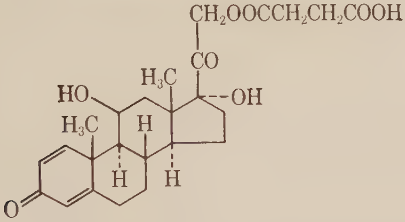
Procedure—Proceed as directed under *Salts of Organic Nitrogenous Bases*, page 865, diluting 20.0 ml. each of the *Standard preparation* and of the *Assay preparation* to 50.0 ml. with 0.5 *N* sulfuric acid, and determining the absorbance at 286 mμ. Calculate the quantity, in mg., of $C_{17}H_{27}NO_3.HCl$ in the portion of the Jelly taken by the formula $0.1C \times A_U/A_S$, in which C is the exact quantity, in mcg., of NF Pramoxine Hydrochloride Reference Standard per ml. of the *Standard preparation*.

Packaging and storage—Preserve Pramoxine Hydrochloride Jelly in tight containers, preferably in collapsible tubes.

Jelly available—Pramoxine Hydrochloride Jelly usually available contains 1 percent of pramoxine hydrochloride.

CATEGORY and APPLICATION—See Pramoxine Hydrochloride.

Prednisolone Succinate



11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(Hydrogen Succinate)

$C_{25}H_{32}O_8$ Mol. wt. 460.53

Prednisolone Succinate contains not less than 98.0 percent and not more than 102.0 percent of $C_{25}H_{32}O_8$, calculated on the dried basis.

Description—Prednisolone Succinate occurs as a fine, creamy white, practically odorless powder with friable lumps. It melts at about 205° with decomposition.

Solubility—Prednisolone Succinate is very slightly soluble in water. It is freely soluble in alcohol and is soluble in acetone.

Identification—

A: Dissolve about 3 mg. of Prednisolone Succinate in 2 ml. of sulfuric acid: a red-amber color is produced which darkens on standing.

B: Add about 2 mg. of Prednisolone Succinate to 2 ml. of perchloric acid, and heat on a steam bath for about 30 seconds: an intense red color is produced which darkens on standing. The addition of a few drops of water does not discharge the color.

C: Add a mixture of 10 mg. of Prednisolone Succinate and 10 mg. of resorcinol to 0.3 ml. of sulfuric acid, and heat over a small flame until sulfur trioxide fumes just begin to evolve. Cool, cautiously add 2 ml. of water, and pour the solution into a mixture of 10 ml. of sodium hydroxide T.S. and 100 ml. of water: an orange color with a green fluorescence is produced which disappears when the solution is acidified.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Prednisolone Succinate, previously dried in vacuum at 65° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Prednisolone Succinate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 30,000 solution of Prednisolone Succinate in methanol exhibits maxima and minima at the same wavelengths as that of NF Prednisolone Succinate Reference Standard, similarly measured, and the respective absorptivities calculated on the dried basis, at the point of maximum absorbance occurring at about 243 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Prednisolone Succinate, calculated on the dried basis, determined in a solution in dioxane containing 67 mg. of Prednisolone Succinate in each 10 ml., is between +99° and +104°.

Loss on drying, page 814—Dry Prednisolone Succinate in vacuum at 65° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 100 mg. of Prednisolone Succinate is negligible.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Prednisolone Succinate Reference Standard, previously dried in vacuum at 65° for 3 hours.

Test preparation—Weigh accurately about 80 mg. of Prednisolone Succinate, previously dried in vacuum at 65° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of *n*-butanol, acetic acid, and water (5:4:1), and determining the absorbances at the maximum at about 243 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Prednisolone Succinate taken: not more than 3 percent is found.

Assay—Dissolve about 1 g. of Prednisolone Succinate, accurately weighed, in 250 ml. of alcohol, previously adjusted to pH 10.5 with 0.1 N sodium hydroxide. Titrate with 0.1 N sodium hydroxide determining the end-point potentiometrically using suitable electrodes, and maintaining an atmosphere of nitrogen over the surface of the solution throughout the titration. Each ml. of 0.1 N sodium hydroxide is equivalent to 46.05 mg. of $C_{25}H_{32}O_8$.

Packaging and storage—Preserve Prednisolone Succinate in tight containers.

CATEGORY and DOSE—See Prednisolone Sodium Succinate for Injection.

Prednisolone Sodium Succinate for Injection*

Prednisolone Sodium Succinate for Injection is sterile prednisolone sodium succinate prepared from prednisolone succinate with the aid of sodium carbonate. It contains suitable buffers. It contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{28}O_5$ (prednisolone).

Description—Prednisolone Sodium Succinate for Injection occurs as a creamy white powder with friable lumps, having a slight odor.

Completeness of solution—A 250-mg. portion of Prednisolone Sodium Succinate for Injection dissolves in 10 ml. of water to yield a clear solution.

Identification—Transfer about 50 mg. of Prednisolone Sodium Succinate for Injection to a separator with the aid of 20 ml. of water, add 2 ml. of diluted hydrochloric acid, and extract with 25 ml. of chloroform. Filter the extract into a suitable beaker, evaporate to dryness on a steam bath, and dry the residue at 60° for 1 hour: the residue so obtained meets the requirements for *Infrared absorption* under *Prednisolone Succinate,* page 585.

pH, page 824—The pH of the solution prepared in the test for *Completeness of solution* is between 6.7 and 7.0.

Loss on drying, page 814—Dry Prednisolone Sodium Succinate for Injection at 105° for 3 hours: it loses not more than 2 percent of its weight.

Content uniformity, *Method I,* page 798—Prednisolone Sodium Succinate for Injection meets the requirements of the content uniformity test for sterile solids.

Other requirements—Prednisolone Sodium Succinate for Injection meets the requirements for *Sterility tests* and for *Labeling* under *Injections,* page 810.

Assay—

Standard preparation—Dissolve about

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* Patented. See notice, page ii.

64 mg. of NF Prednisolone Succinate Reference Standard, accurately weighed, in sufficient alcohol to make 200.0 ml. Dilute 4.0 ml. of this solution to 100.0 ml. with alcohol, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered 50-ml. conical flask.

Assay preparation—Transfer an accurately weighed portion of Prednisolone Sodium Succinate for Injection, equivalent to about 50 mg. of prednisolone, to a 200-ml. volumetric flask, add alcohol to volume, and mix thoroughly. Dilute 4.0 ml. of this suspension to 100.0 ml. with alcohol, and mix. Pipet 20.0 ml. of this solution into a glass-stoppered 50-ml. conical flask.

Procedure—Proceed as directed under *Steroid Assay,* page 876. Calculate the quantity of prednisolone in the portion of the sample taken by the formula $5C \times 0.7827 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Prednisolone Succinate Reference Standard in the *Standard preparation,* and 0.7827 is the ratio of the molecular weight of prednisolone to that of prednisolone succinate.

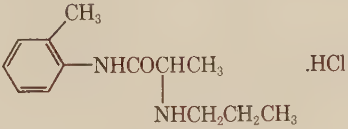
Packaging and storage—Preserve Prednisolone Sodium Succinate for Injection in *Containers for Sterile Solids* as described under *Injections,* page 810.

Size available—Prednisolone Sodium Succinate for Injection usually available contains an amount of prednisolone sodium succinate equivalent to the following amount of prednisolone: 50 mg.

CATEGORY—Glucocorticoid.

USUAL DOSE—Intravenous, the equivalent of **25** or **50 mg.** of prednisolone given over a 1-minute period, repeated every 3 or 4 hours for four doses.

Prilocaine Hydrochloride*



2-(Propylamino)-*o*-propionotoluidide Hydrochloride

$C_{13}H_{20}N_2O.HCl$ Mol. wt. 256.78

Prilocaine Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $C_{13}H_{20}N_2O.HCl$, calculated on the dried basis.

Description—Prilocaine Hydrochloride occurs as a white, odorless, crystalline powder having a bitter taste.

Solubility—Prilocaine Hydrochloride is freely soluble in water and in alcohol. It is slightly soluble in chloroform, very slightly soluble in acetone, and practically insoluble in ether.

Identification—

A: Dissolve about 300 mg. of Prilocaine Hydrochloride in 5 ml. of water, add 4 ml. of ammonia T.S., and extract with 50 ml. of chloroform. Filter the extract, and evaporate the filtrate on a steam bath with the aid of a current of air. Dissolve about 100 mg. of the prilocaine base so obtained in 1 ml. of alcohol, add 10 drops of cobaltous chloride T.S., and shake for 2 minutes: a bright green color develops, and a precipitate forms.

B: Dissolve about 100 mg. of the prilocaine base obtained in *Identification test A* in a mixture of 5 ml. of water and 1 ml. of diluted nitric acid, add 3 ml. of mercuric nitrate T.S., and heat nearly to boiling: a yellow or yellowish green color develops.

C: Dissolve about 100 mg. of Prilocaine Hydrochloride in 3 ml. of water, make the solution alkaline with ammonia T.S., and filter: the filtrate responds to the tests for *Chloride,* page 808.

Melting range, page 814—Prilocaine Hydrochloride melts between 166° and 169°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Prilocaine Hydrochloride, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Prilocaine Hydrochloride Reference Standard, similarly measured.

Loss on drying, page 814—Dry Prilocaine Hydrochloride at 105° for 4 hours: it loses not more than 0.3 percent of its weight.

Residue on ignition, page 858—Prilocaine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Heavy metals—Dissolve about 200 mg. of Prilocaine Hydrochloride in 20 ml. of water, add 2 ml. of diluted hydrochloric acid, and saturate the solution with hydrogen sulfide: no color or precipitate is produced.

Assay—Dissolve about 500 mg. of Prilocaine Hydrochloride, accurately weighed, in 50 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S. and

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* Patented. See notice, page ii.

2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 25.68 mg. of $C_{13}H_{20}N_2O.HCl$.

Packaging and storage—Preserve Prilocaine Hydrochloride in well-closed containers.

Category—Local anesthetic.

Usual dose range—Therapeutic nerve block, **3 to 5 ml.** of a **1 percent** or **2 percent** solution; infiltration, **20 to 30 ml.** of a **1** or **2 percent** solution; regional anesthesia, peridural, and caudal, **15 to 20 ml.** of a **3 percent** solution or **20 to 30 ml.** of a **1** or **2 percent** solution; for infiltration and nerve block in dentistry, **0.5 to 5.0 ml.** of a **4 percent** solution.

Prilocaine Hydrochloride Injection

Prilocaine Hydrochloride Injection is a sterile solution of prilocaine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O.HCl$.

Identification—Prilocaine Hydrochloride Injection responds to the *Identification tests* under *Prilocaine Hydrochloride*, page 587.

pH, page 824—The pH of Prilocaine Hydrochloride Injection is between 6.0 and 7.0.

Other requirements—Prilocaine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—Transfer to a separator an accurately measured volume of Prilocaine Hydrochloride Injection, equivalent to about 200 mg. of prilocaine hydrochloride, add 2 ml. of sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform, filtering each extract through chloroform-moistened paper. Concentrate the combined filtrates to about 10 ml. on a steam bath with the aid of a current of air, add 40 ml. of glacial acetic acid and 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 25.68 mg. of $C_{13}H_{20}N_2O.HCl$.

Packaging and storage—Preserve Prilocaine Hydrochloride Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Prilocaine Hydrochloride Injection usually available contains the following amounts of prilocaine hydrochloride: 1 and 2 percent in 30 ml., 3 percent in 20 ml., and 4 percent in 1.8 ml.

Category and Dose—See Prilocaine Hydrochloride.

Procaine Hydrochloride and Levonordefrin Injection

Procaine Hydrochloride and Levonordefrin Injection is a sterile solution of procaine hydrochloride and levonordefrin in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O_2.HCl$ (procaine hydrochloride), and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (levonordefrin).

Identification—

A: Mix 10 ml. of Procaine Hydrochloride and Levonordefrin Injection with 10 ml. of diluted hydrochloric acid, cool to 0° in an ice bath, add 5 ml. of a solution of sodium nitrite (1 in 5), stirring gently, and 2 ml. of a solution of 100 mg. of beta-naphthol in 5 ml. of sodium hydroxide T.S., and observe immediately: a bright orange-red precipitate is produced (*presence of a primary aminophenyl group*).

B: Procaine Hydrochloride and Levonordefrin Injection responds to the tests for *Chloride*, page 808.

pH, page 824—The pH of Procaine Hydrochloride and Levonordefrin Injection is between 3.5 and 5.0.

Other requirements—Procaine Hydrochloride and Levonordefrin Injection meets the requirements under *Injections*, page 810.

Assay for procaine hydrochloride—Transfer an accurately measured volume of Procaine Hydrochloride and Levonordefrin Injection, equivalent to about 100 mg. of procaine hydrochloride, to a 125-ml. separator containing 25 ml. of chloroform and 10 ml. of water. Add 5 ml. of sodium carbonate T.S., shake well, allow the layers to separate, and transfer the chloroform layer to a second separator. Extract the aqueous solution with two additional 10-ml. portions of chloroform, adding the extracts to the second separator. Extract the combined chloroform extracts with 35 ml. of 2 *N* hydrochloric acid. Transfer the chloroform to another separator, and transfer the aqueous layer to a 100-ml. volumetric flask. Extract the chloroform with two 30-ml. portions of 2 *N* hydrochloric acid, add to the volumetric flask, dilute to volume with 2 *N* hydrochloric acid, and mix. Transfer 15.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 2 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of USP Procaine Hydrochloride Reference Standard, in the same medium, at a concentration of about 150 mcg. per ml., in 1-cm. cells, at the maximum at about 272 mμ, using water as the blank. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2.HCl$ in each ml. of the Injection taken by the formula $0.667 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Injection taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Assay for levonordefrin—Prepare a *Ferro-citrate Solution*, a *Buffer Solution*, and a *Standard Preparation* as directed under *Epinephrine Assay*, page 803.

Assay preparation—Proceed as directed for *Assay preparation* under *Epinephrine Assay*, page 803, except change epinephrine to levonordefrin.

Procedure—Proceed as directed for *Procedure* under *Epinephrine Assay*, page 803. Calculate the quantity, in mg., of $C_9H_{13}NO_3$ in each ml. of the Injection taken by the formula $0.01 \times (C/V) \times 0.5497 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Epinephrine Bitartrate Reference Standard in the *Standard Preparation*, V is the volume, in ml., of the Injection taken, and 0.5497 is the factor converting epinephrine bitartrate to levonordefrin.

Packaging and storage—Preserve Procaine Hydrochloride and Levonordefrin Injection in single-dose containers, preferably of Type I glass.

Injection available—Procaine Hydrochloride and Levonordefrin Injection usually available contains the following amounts of procaine hydrochloride and levonordefrin: 2 percent procaine hydrochloride and 1 in 20,000 levonordefrin in 2-ml. cartridges.

CATEGORY—Local anesthetic (dental).

Procaine and Phenylephrine Hydrochlorides Injection

Procaine and Phenylephrine Hydrochlorides Injection is a sterile solution of procaine hydrochloride and phenylephrine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O_2.HCl$ (procaine hydrochloride), and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_2.HCl$ (phenylephrine hydrochloride).

Identification—

A: Mix 10 ml. of Procaine and Phenylephrine Hydrochlorides Injection with 10 ml. of diluted hydrochloric acid, cool to 0° in an ice bath, add 5 ml. of a solution of sodium nitrite (1 in 5), stirring gently, and 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S., and observe immediately: a bright orange-red precipitate is produced (*presence of a primary aminophenyl group*).

B: Procaine and Phenylephrine Hydrochlorides Injection responds to the tests for *Chloride*, page 808.

pH, page 824—The pH of Procaine and Phenylephrine Hydrochlorides Injection is between 3.0 and 5.5.

Other requirements—Procaine and Phenylephrine Hydrochlorides Injection meets the requirements under *Injections*, page 810.

Assay for procaine hydrochloride—Transfer an accurately measured volume of Procaine and Phenylephrine Hydrochlorides Injection, equivalent to about 100 mg. of procaine hydrochloride, to a 125-ml. separator containing 25 ml. of chloroform and 10 ml. of water. Add 5 ml. of sodium carbonate T.S., shake well, allow the layers to separate, and transfer the chloroform layer to a second separator. Extract the aqueous solution with two additional 10-ml. portions of chloroform, adding the extracts to the second separator. Extract the combined chloroform extracts with 35 ml. of 2 *N* hydrochloric acid. Transfer the chloroform to another separator, and transfer the aqueous layer to a 100-ml. volumetric flask. Extract the chloroform with two 30-ml. portions of 2 N hydrochloric acid, add to the volumetric flask, dilute to volume with 2 N hydrochloric acid, and mix. Transfer 15.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 2 N hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of USP Procaine Hydrochloride Reference Standard, in the same medium, at a concentration of about 150 mcg. per ml., in 1-cm. cells, at the maximum at about 272 mμ, using water as the blank. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2.HCl$ in each ml. of the Injection taken by the formula $0.667 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Injection taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Assay for phenylephrine hydrochloride—

Standard preparation—Transfer about 33 mg. of USP Phenylephrine Hydrochloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix.

Assay preparation—Use Procaine and Phenylephrine Hydrochlorides Injection undiluted.

Procedure—Transfer 1.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 100-ml. volumetric flasks, and transfer 1.0 ml. of water to a third flask to serve as a blank. To each flask add 5.0 ml. of potassium ferricyanide solution (1 in 50) followed by 5.0 ml. of 0.025 M 4-aminoantipyrine, and mix. Dilute to volume with 0.01 M sodium bicarbonate, mix, and allow to stand for exactly 15 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 500 mμ, with a suitable spectrophotometer, using the reagent blank to set the instrument. Calculate the quantity, in mg., of $C_9H_{13}NO_2.HCl$ in the Injection taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, A_U is the absorbance of the *Assay preparation*, and A_S is the absorbance of the *Standard preparation*.

Packaging and storage—Preserve Procaine and Phenylephrine Hydrochlorides Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Procaine and Phenylephrine Hydrochlorides Injection usually available contains the following amounts of procaine hydrochloride and phenylephrine hydrochloride: 2 or 4 percent procaine hydrochloride and 1:2500 phenylephrine hydrochloride.

CATEGORY—Local anesthetic (dental).

Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection

Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection is a sterile solution of procaine hydrochloride, propoxycaine hydrochloride, and levarterenol bitartrate in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O_2.HCl$ (procaine hydrochloride), not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{16}H_{26}N_2O_3.HCl$ (propoxycaine hydrochloride), and an amount of levarterenol bitartrate ($C_8H_{11}NO_3.C_4H_6O_6.H_2O$) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_8H_{11}NO_3$ (levarterenol).

Identification—

A: Cool a mixture of 10 ml. of Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection and 10 ml. of diluted hydrochloric acid to 0° in an ice bath, add 5 ml. of a solution of sodium nitrite (1 in 5), stirring gently, and 2 ml. of a solution of 100 mg. of beta-naphthol in 5 ml. of sodium hydroxide T.S., and observe immediately: a bright orange-red precipitate is produced (*presence of a primary aminophenyl group*).

B: Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection responds to the tests for *Chloride*, page 808.

pH, page 824—The pH of Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection is between 3.5 and 5.0.

Other requirements—Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection meets the requirements under *Injections*, page 810.

Assay for procaine and propoxycaine hydrochlorides—

Standard procaine hydrochloride preparation—Prepare, by quantitative and stepwise dilution, a solution in 2 *N* hydrochloric acid containing about 200 mcg. of USP Procaine Hydrochloride Reference Standard, accurately weighed, in each ml.

Standard propoxycaine hydrochloride preparation—Prepare, by quantitative and stepwise dilution, a solution in 2 *N* hydrochloric acid containing about 50 mcg. of NF Propoxycaine Hydrochloride Reference Standard, accurately weighed, in each ml.

Assay preparation—Transfer an accurately measured volume of Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection, equivalent to about 100 mg. of procaine hydrochloride, to a 125-ml. separator containing 25 ml. of chloroform and 10 ml. of water. Add 5 ml. of sodium carbonate T.S., shake vigorously, allow the layers to separate, and transfer the chloroform layer to a second separator. Extract the aqueous layer with two 10-ml. portions of chloroform, adding the extracts to the second separator. Extract the combined chloroform extracts with 35 ml. of 2 *N* hydrochloric acid, transfer the chloroform to a third separator, and transfer the acid extract to a 100-ml. volumetric flask. Extract the chloroform with two 10-ml. portions of 2 *N* hydrochloric acid, add the acid extracts to the volumetric flask, dilute to volume with 2 *N* hydrochloric acid, and mix. Transfer 15.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with 2 *N* hydrochloric acid, and mix.

Procedure—Concomitantly determine the absorbance of the *Standard preparations* and of the *Assay preparation*, in 1-cm. cells, at 296 mμ and at 272 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbances of the *Standard propoxycaine hydrochloride preparation* at 296 mμ and at 272 mμ as A_1 and A_2, respectively; record the absorbances of the *Standard procaine hydrochloride preparation* at 296 mμ and at 272 mμ as A_3 and A_4, respectively; and record the absorbance of the *Assay preparation* at 296 mμ and at 272 mμ as A_{296} and A_{272}, respectively. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2 . HCl$ (procaine hydrochloride) in each ml. of the Injection taken by the formula $0.667 \times (C/V) \times (A_{272}A_1 - A_{296}A_2)/(A_1A_4 - A_2A_3)$, in which C is the exact concentration, in mcg. per ml., of the *Standard procaine hydrochloride preparation*, and V is the volume, in ml., of the Injection taken.

Calculate the quantity, in mg., of $C_{16}H_{26}N_2O_3 . HCl$ (propoxycaine hydrochloride) in each ml. of the Injection taken by the formula $0.667 \times (C/V) \times (A_{296}A_4 - A_{272}A_3)/(A_1A_4 - A_2A_3)$, in which C is the exact concentration, in mcg. per ml., of the *Standard propoxycaine hydrochloride preparation*, and V is the volume, in ml., of the Injection taken.

Assay for levarterenol—Prepare a *Ferrocitrate Solution*, a *Buffer Solution*, and a *Standard Preparation* as directed under *Epinephrine Assay*, page 803.

Assay preparation—Proceed as directed for *Assay Preparation* under *Epinephrine Assay*, page 803, except change epinephrine to levarterenol, and take an accurately measured volume of Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection equivalent to about 200 mcg. of levarterenol.

Procedure—Proceed as directed for *Procedure* under *Epinephrine Assay*, page 803. Calculate the quantity, in mg., of $C_8H_{11}NO_3$ in each ml. of the Injection taken by the formula $0.01 \times (C/V) \times 0.5074 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Epinephrine Bitartrate Reference Standard in the *Standard Preparation*, V is the volume, in ml., of the Injection taken, and 0.5074 is the factor converting epinephrine bitartrate to levarterenol.

Packaging and storage—Preserve Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Procaine and Propoxycaine Hydrochlorides and Levarterenol Bitartrate Injection usually available contains the following amounts of procaine hydrochloride, propoxycaine hydrochloride, and levarterenol: 2 percent procaine hydrochloride, 0.4 percent propoxycaine hydrochloride, and 1 in 30,000 levarterenol, in 1.8-ml. and 2.2-ml. cartridges and 30-ml. vials.

CATEGORY—Local anesthetic (dental).

Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection

Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection is a sterile solution of propoxycaine hydrochloride, procaine hydrochloride, and levonordefrin in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{12}H_{20}N_2O_2 . HCl$ (procaine hydrochloride), not less than 95.0 percent and not more than 105.0

percent of the labeled amount of $C_{16}H_{26}N_2O_3.HCl$ (propoxycaine hydrochloride) and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (levonordefrin).

Identification—

A: Cool a mixture of 10 ml. of Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection and 10 ml. of diluted hydrochloric acid to 0° in an ice bath, add 5 ml. of a solution of sodium nitrite (1 in 5), stirring gently, and 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S., and observe immediately: a bright orange-red precipitate is produced (*presence of a primary aromatic amino group*).

B: Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection responds to the test for *Chloride,* page 808.

Other requirements—Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection meets the requirements under *Injections,* page 810.

Assay for propoxycaine and procaine hydrochlorides—

Standard propoxycaine hydrochloride preparation—Prepare, by quantitative and stepwise dilution, a solution, in 2 *N* hydrochloric acid, containing about 40 mcg. of NF Propoxycaine Hydrochloride Reference Standard in each ml.

Sample preparation—Transfer an accurately measured volume of Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection, equivalent to about 100 mg. of propoxycaine hydrochloride, to a 125-ml. separator containing 25 ml. of chloroform. Add 5 ml. of sodium carbonate T.S., shake well, let separate, and transfer the chloroform layer to a second separator. Extract the aqueous solution with two additional 10-ml. portions of chloroform, adding the extracts to the second separator. Extract the combined chloroform extracts with 35 ml. of 2 *N* hydrochloric acid. Transfer the chloroform layer to another separator, and transfer the aqueous layer to a 50-ml. volumetric flask. Extract the chloroform with 10 ml. of 2 *N* hydrochloric acid, and add the aqueous layer to the volumetric flask. Dilute the combined acid extracts to volume with 2 *N* hydrochloric acid, and mix.

Procedure for propoxycaine hydrochloride—Pipet 2.0 ml. of the *Sample preparation* into a 100-ml. volumetric flask, dilute to volume with 2 *N* hydrochloric acid, and mix. Use this solution as the *Propoxycaine hydrochloride sample solution.* Concomitantly determine the absorbance of this solution and of the *Standard propoxycaine hydrochloride preparation* in 1-cm. cells at 300 $m\mu$, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{16}H_{26}N_2O_3.HCl$ in each ml. of the Injection taken, by the formula $2.5 \times (C/V_S) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of NF Propoxycaine Hydrochloride in the *Standard propoxycaine hydrochloride preparation,* V_S is the volume of the Injection taken, A_U is the absorbance of the *Propoxycaine hydrochloride sample solution,* and A_S is the absorbance of the *Standard propoxycaine hydrochloride preparation.*

Procedure for procaine hydrochloride—Pipet 40.0 ml. of the *Sample preparation* into a 250-ml. beaker, add 2 g. of potassium bromide and 60 ml. of ice-cold water, and titrate with 0.1 *M* sodium nitrite, determining the end-point by spotting on starch iodide paper. Perform a blank determination, using 40 ml. of 2 *N* hydrochloric acid in place of the *Sample preparation,* and make any necessary correction. The corrected volume of 0.1 *M* sodium nitrite is equivalent to the total anesthetics in the sample taken. Calculate the quantity of $C_{13}H_{20}N_2O_2.HCl$, in each ml. of the injection taken, by the formula

$$\frac{272.78\,(M) \times 50/40}{V_S} \times \left[V_T - \frac{40/50\,V_S P_X}{330.86\,(M)}\right],$$

in which M is the exact molarity of the 0.1 *M* sodium nitrite solution, V_T is the corrected volume of 0.1 *M* sodium nitrite consumed, V_S is the volume of the Injection taken, and P_X is the previously determined concentration, in mg., of propoxycaine hydrochloride per ml. of the Injection.

Assay for levonordefrin—Prepare a *Ferrocitrate solution,* a *Buffer solution,* and a *Standard preparation* as directed under *Epinephrine Assay,* page 803.

Assay preparation—Proceed as directed for *Assay preparation* under *Epinephrine Assay,* page 803, except change epinephrine to levonordefrin.

Procedure—Proceed as directed for *Procedure* under *Epinephrine Assay,* page 803.

Packaging and storage—Preserve Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection in single-dose containers, preferable of Type I glass.

Injections available—Procaine and Propoxycaine Hydrochlorides and Levonordefrin Injection usually available contains the following amounts of propoxycaine hydrochloride, procaine hydrochloride, and levonordefrin: 0.4 percent propoxycaine hydrochloride, 2 percent procaine hydrochloride, and 1 in 20,000 levonordefrin, in 2-ml. cartridges.

Category and Dose—Local anesthetic (dental).

Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection

Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection is a sterile solution of procaine hydrochloride, tetracaine hydrochloride, and levarterenol bitartrate in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O_2 . HCl$ (procaine hydrochloride), not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{15}H_{24}N_2O_2 . HCl$ (tetracaine hydrochloride), and an amount of levarterenol bitartrate ($C_8H_{11}NO_3 . C_4H_6O_6 . H_2O$) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_8H_{11}NO_3$ (levarterenol).

Identification—

A: Mix 10 ml. of Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection with 10 ml. of diluted hydrochloric acid, cool to 0° in an ice bath, add 5 ml. of a solution of sodium nitrite (1 in 5), stirring gently, and 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S., and observe immediately: a bright orange-red precipitate is produced (*presence of a primary aminophenyl group*).

B: Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection responds to the tests for *Chloride*, page 808.

C: To about 5 ml. of Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection add 1 drop of ferric chloride T.S.: a green color develops (*presence of levarterenol bitartrate*).

pH, page 824—The pH of Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection is between 3.5 and 5.0.

Other requirements—Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection meets the requirements under *Injections*, page 810.

Assay for procaine hydrochloride—Transfer 25.0 ml. of Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection to a 250-ml. beaker, add 10 ml. of 6 *N* hydrochloric acid, 15 ml. of water, and 1.0 ml. of formaldehyde solution, and allow to stand for 3 minutes. Titrate with 0.1 *M* sodium nitrite, using starch iodide paper as an external indicator. Perform a blank determination, and make any necessary correction. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2 . HCl$ in each ml. of the Injection by the formula $(V_2M_2 - 0.5V_1M_1) \times (272.78/25)$, in which V_2 is the volume, in ml., and M_2 the exact molarity, respectively, of the 0.1 *M* sodium nitrite solution used in the titration, and V_1 and M_1 are as defined under *Assay for tetracaine hydrochloride*.

Assay for tetracaine hydrochloride—Transfer 50.0 ml. of Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection to a 100-ml. beaker, add 5 g. of sodium acetate and 5 ml. of isopropyl alcohol, and stir until the sodium acetate is dissolved. Add 1.5 ml. of a solution of potassium thiocyanate (75 in 100), and stir while cooling in an ice bath. Keep in the ice bath for 1 hour, stirring about 4 times during this period. Do not stir excessively. Prepare a filtering crucible with double suitable filter paper, connect to a suction flask, and moisten the paper with a few drops of the clear supernatant liquid. Remove the excess liquid by suction. Filter the mixture, and dry by suction. Transfer the entire contents of the crucible to the original beaker, and rinse the crucible with 10 ml. of 6 *N* hydrochloric acid, followed by 30 ml. of water. Transfer the rinsings to the beaker. Cool in ice, and titrate with 0.02 *M* sodium nitrite, using starch iodide paper as an external indicator. Perform a blank determination, using 10 ml. of 6 *N* hydrochloric acid and 30 ml. of water, and make any necessary correction. Calculate the quantity, in mg., of $C_{15}H_{24}N_2O_2 . HCl$ in each ml. of the Injection by the formula $V_1 \times M_1 \times (300.83/50)$, in which V_1 is the volume, in ml., and M_1 the exact molarity, respectively, of the 0.02 *M* sodium nitrite solution.

Assay for levarterenol—Prepare a *Ferrocitrate Solution*, a *Buffer Solution*, and a *Standard Preparation* as directed under *Epinephrine Assay*, page 803.

Assay preparation—Proceed as directed for *Assay Preparation* under *Ephinephrine Assay*, page 803, except change epinephrine to levarterenol.

Procedure—Proceed as directed for *Procedure* under *Epinephrine Assay*, page 803. Calculate the quantity, in mg., of $C_8H_{11}NO_3$ (levarterenol) in each ml. of the Injection taken by the formula $0.01 \times (C/V) \times 0.5074 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Epinephrine Bitartrate Reference Standard in the *Standard Preparation*, V is the volume, in ml., of the Injection taken, and 0.5074 is the factor converting epinephrine bitartrate to levarterenol.

Packaging and storage—Preserve Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection in single-dose containers, preferably of Type I glass.

Injection available—Procaine and Tetracaine Hydrochlorides and Levarterenol Bitartrate Injection usually available contains the following amounts of procaine hydrochloride, tetracaine hydrochloride, and levarterenol (as the bitartrate): 2 percent procaine hydrochloride, 0.15 percent tetracaine hydrochloride, and 1 in 30,000 levarterenol, in 2-ml. cartridges.

Category—Local anesthetic (dental).

Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection

Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection is a sterile solution of procaine hydrochloride, tetracaine hydrochloride, and levonordefrin in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O_2 . HCl$ (procaine hydrochloride), not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{15}H_{24}N_2O_2 . HCl$ (tetracaine hydrochloride), and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (levonordefrin).

Identification—

A: Mix 10 ml. of Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection with 10 ml. of diluted hydrochloric acid, cool to 0° in an ice bath, add 5 ml. of a solution of sodium nitrite (1 in 5), stirring gently, and 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S., and observe immediately: a bright orange-red precipitate is produced (*presence of a primary aminophenyl group*).

B: Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection responds to the tests for *Chloride*, page 808.

C: To about 25 ml. of Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection add 1 drop of ferric chloride T.S.: the solution immediately turns a light green and changes to a light blue within 1 minute. Add 2 drops of diluted hydrochloric acid: the color reverts to light green (*presence of levonordefrin*).

pH, page 824—The pH of Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection is between 3.5 and 5.0.

Other requirements—Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection meets the requirements under *Injections*, page 810.

Assay for procaine hydrochloride—Transfer 25.0 ml. of Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection to a 250-ml. beaker, add 10 ml. of 6 N hydrochloric acid, 15 ml. of water, and 1.0 ml. of formaldehyde solution, and allow to stand 3 minutes. Titrate with 0.1 M sodium nitrite, using starch iodide paper as an external indicator. Perform a blank determination, and make any necessary correction. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2 . HCl$ in each ml. of the Injection by the formula $(V_2M_2 - 0.5V_1M_1) \times (272.78/25)$, in which V_2 is the volume, in ml., and M_2 the exact molarity, respectively, of the 0.1 M sodium nitrite solution used in the titration, and V_1 and M_1 are as defined under *Assay for tetracaine hydrochloride*.

Assay for tetracaine hydrochloride—Transfer 50.0 ml. of Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection to a 100-ml. beaker, add 5 g. of sodium acetate and 5 ml. of isopropyl alcohol, and stir until the sodium acetate is dissolved. Add 1.5 ml. of a solution of potassium thiocyanate (75 in 100), and stir while cooling in an ice bath. Keep in the ice bath for 1 hour, stirring about 4 times during the period. Do not stir excessively. Prepare a filtering crucible with double suitable filter paper, connect to a suction flask, and moisten the paper with a few drops of the clear supernatant liquid. Remove the excess liquid by suction. Filter the mixture, and dry by suction. Transfer the entire contents of the crucible to the original beaker, and rinse the crucible with 10 ml. of 6 N hydrochloric acid, followed by 30 ml. of water. Transfer the rinsings to the beaker. Cool in ice, and titrate with 0.02 M sodium nitrite, using starch iodide paper as an external indicator. Perform a blank determination using 10 ml. of 6 N hydrochloric acid and 30 ml. of water, and make any necessary correction. Calculate the quantity, in mg., of $C_{15}H_{24}N_2O_2.HCl$ in each ml. of the Injection by the formula $V_1 \times M_1 \times (300.83/50)$, in which V_1 is the volume, in ml., and M_1 the exact molarity, respectively, of the 0.02 M sodium nitrite used in the titration.

Assay for levonordefrin—Prepare a

Ferro-citrate Solution, a *Buffer Solution*, and a *Standard Preparation* as directed under *Epinephrine Assay*, page 803.

Assay preparation—Proceed as directed for *Assay preparation* under *Epinephrine Assay*, page 803, except change epinephrine to levonordefrin.

Procedure—Proceed as directed for *Procedure* under *Epinephrine Assay*, page 803. Calculate the quantity, in mg., of $C_9H_{13}NO_3$ (levonordefrin) in each ml. of the Injection taken by the formula $0.01 \times (C/V) \times 0.5497 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Epinephrine Bitartrate Reference Standard in the *Standard Preparation*, V is the volume, in ml., of the Injection taken, and 0.5497 is the factor converting epinephrine bitartrate to levonordefrin.

Packaging and storage—Preserve Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Procaine and Tetracaine Hydrochlorides and Levonordefrin Injection usually available contains the following amounts of procaine hydrochloride, tetracaine hydrochloride, and levonordefrin: 2 percent procaine hydrochloride, 0.15 percent tetracaine hydrochloride, and 1 in 20,000 levonordefrin in 2-ml. cartridges and 30-ml. vials.

CATEGORY—Local anesthetic (dental).

Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection

Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection is a sterile solution of procaine hydrochloride, tetracaine hydrochloride, and phenylephrine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{13}H_{20}N_2O_2.HCl$ (procaine hydrochloride), not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{15}H_{24}N_2O_2.HCl$ (tetracaine hydrochloride), and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_2.HCl$ (phenylephrine hydrochloride).

Identification—

A: Mix 10 ml. of Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection with 10 ml. of diluted hydrochloric acid, cool to 0° in an ice bath, add 5 ml. of a solution of sodium nitrite (1 in 5), stirring gently, and 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S., and observe immediately: a bright orange-red precipitate is produced (*presence of a primary aminophenyl group*).

B: Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection responds to the tests for *Chloride*, page 808.

pH, page 824—The pH of Procaine, Tetracaine, and Phenylephrine Hydrochlorides Injection is 3.5 to 5.0.

Other requirements—Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection meets the requirements under *Injections*, page 810.

Assay for procaine hydrochloride—Transfer 25.0 ml. of Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection to a 250-ml. beaker, add 10 ml. of 6 N hydrochloric acid, 15 ml. of water, and 1.0 ml. of formaldehyde solution, and allow to stand for 3 minutes. Titrate with 0.1 M sodium nitrite, determining the end-point by spotting on starch iodide paper. Calculate the quantity, in mg., of $C_{13}H_{20}N_2O_2.HCl$ in each ml. of the Injection by the formula $(V_2M_2 - 0.5V_1M_1) \times (272.78/25)$, in which V_2 is the volume, in ml., and M_2 the exact molarity, respectively, of the 0.1 M sodium nitrite solution used in the titration, and V_1 and M_1 are as defined under *Assay for tetracaine hydrochloride*.

Assay for tetracaine hydrochloride—Transfer 50.0 ml. of Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection to a 100-ml. beaker, add 5 g. of sodium acetate and 5 ml. of isopropyl alcohol, and stir until the sodium acetate is dissolved. Add 1.5 ml. of a solution of potassium thiocyanate (75 in 100), and stir while cooling in an ice bath. Keep in the ice bath for 1 hour, stirring about 4 times during the period. Do not stir excessively. Prepare a filtering crucible with a double filter paper, wet the paper with a few drops of the clear supernatant liquid, and suck out the excess. Filter the precipitated tetracaine thiocyanate, and suck dry on the filter. Transfer the paper and precipitate to the original beaker, and rinse the crucible with 10 ml. of 6 N hydrochloric acid, followed by 30 ml. of water, adding the rinsings to the beaker containing the paper and precipitate. Cool in ice, and titrate with 0.02 M sodium nitrite, determining the end-point by spotting on starch iodide paper. Perform a blank determination, using 10 ml. of

6 *N* hydrochloric acid, and 30 ml. of water, and make any necessary correction. Calculate the quantity, in mg., of $C_{15}H_{24}N_2O_2 \cdot HCl$ in each ml. of the Injection by the formula $V_1 \times M_1 \times (300.83/50)$, in which V_1 is the volume, in ml., and M_1 the exact molarity, respectively, of the 0.02 *M* sodium nitrite solution used in the titration.

Assay for phenylephrine hydrochloride—

Standard preparation—Transfer about 33 mg. of USP Phenylephrine Hydrochloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix.

Assay preparation—Use Procaine, Tetracaine, and Phenylephrine Hydrochlorides Injection undiluted.

Procedure—Transfer 1.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 100-ml. volumetric flasks, and transfer 1.0 ml. of water to a third flask to serve as a blank. To each flask add 5.0 ml. of potassium ferricyanide solution (1 in 50) followed by 5.0 ml. of 0.025 *M* 4-aminoantipyrine, and mix. Dilute to volume with 0.01 *M* sodium bicarbonate, mix, and allow to stand for exactly 15 minutes. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 500 mμ, with a suitable spectrophotometer, using the reagent blank to set the instrument. Calculate the quantity, in mg., of $C_9H_{13}NO_2 \cdot HCl$ in the Injection taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, A_U is the absorbance of the *Assay preparation*, and A_S is the absorbance of the *Standard preparation*.

Packaging and storage—Preserve Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection in single-dose containers, preferably of Type I glass.

Injection available—Procaine, Tetracaine and Phenylephrine Hydrochlorides Injection usually available contains the following: 2 percent of procaine hydrochloride, 0.15 percent of tetracaine hydrochloride, and 1 in 2500 of phenylephrine hydrochloride in 2-ml. cartridges.

Category—Local anesthetic (dental).

Usual dose—Nerve block and infiltration anesthesia, **2 ml.**

Procaine Penicillin G and Sodium Penicillin G for Injection

Procaine Penicillin G and Sodium Penicillin G for Injection is a sterile, dry mixture of procaine penicillin G and sodium penicillin G and one or more suitable, harmless suspending or dispersing agents. It contains not less than 90.0 percent of the labeled amount of penicillin units. It contains sodium penicillin G equivalent to not less than 50,000 units for each 300,000 units of procaine penicillin G. It conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

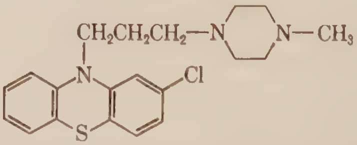
Packaging and storage—Preserve Procaine Penicillin G and Sodium Penicillin G for Injection in single-dose or in multiple-dose containers.

Sizes available—Procaine Penicillin G and Sodium Penicillin G for Injection is usually available as follows: 400,000, 2,000,000 and 4,000,000 units in 1-, 5-, and 10-dose containers.

Category—Antibacterial.

Usual dose—Intramuscular, **400,000 units** one or three times daily as required.

Prochlorperazine*



2-Chloro-10-[3-(4-methyl-1-piperazinyl)propyl]phenothiazine

$C_{20}H_{24}ClN_3S$ Mol. wt. 373.95

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* Patented. See notice, page ii.

Prochlorperazine contains not less than 98.0 percent and not more than 101.0 percent of $C_{20}H_{24}ClN_3S$.

Description—Prochlorperazine is a clear, pale yellow, viscous liquid. It is sensitive to light.

Solubility—Prochlorperazine is very slightly soluble in water. It is freely soluble in alcohol, in chloroform, and in ether.

Identification—Prochlorperazine meets the requirements under *Identification—Organic Nitrogenous Bases,* page 810, using USP Prochlorperazine Maleate Reference Standard as the standard for comparison.

Residue on ignition, page 858—Prochlorperazine yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 400 mg. of Prochlorperazine, accurately weighed, into a 125-ml. conical flask, add 30 ml. of glacial acetic acid, and warm on a steam bath to dissolve the sample. Add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 18.70 mg. of $C_{20}H_{24}ClN_3S$.

Packaging and storage—Preserve Prochlorperazine in tight, light-resistant containers.

CATEGORY—Tranquilizer (major); antiemetic.

USUAL DOSE RANGE—Rectal, **2.5 to 25 mg.**

Prochlorperazine Suppositories

Prochlorperazine Suppositories contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{24}ClN_3S$.

Identification—

A: Transfer a quantity of Prochlorperazine Suppositories, equivalent to about 5 mg. of prochlorperazine, to a test tube, add 4 ml. of dilute hydrochloric acid (1 in 2), warm on a steam bath to melt the suppository mass, and swirl to mix: a pink color develops in the aqueous layer.

B: Transfer a quantity of Prochlorperazine Suppositories, equivalent to about 5 mg. of prochlorperazine, to a test tube, add 5 ml. of dilute sulfuric acid (1 in 2), warm on a steam bath to melt the suppository mass, add 10 ml. of bromine T.S., and mix: essentially no color change occurs (*distinction from chlorpromazine which immediately produces a green color*).

Assay—

Standard preparation—Transfer about 40 mg. of USP Prochlorperazine Maleate Reference Standard, previously dried at 105° for 2 hours and accurately weighed, to a 250-ml. separator containing 75 ml. of ether. Add 0.5 ml. of ammonia T.S., and proceed as directed under *Assay preparation* beginning with "Extract the combined ether solution . . . ."

Assay preparation—Mash and thoroughly mix a sample of not less than 15 Prochlorperazine Suppositories. Transfer an accurately weighed quantity of the mass, equivalent to about 25 mg. of prochlorperazine, to a 100-ml. beaker. Dissolve in 50 ml. of ether, and transfer the solution to a 250-ml. separator, completing the transfer and rinsing of the beaker with three 25-ml. portions of ether. Extract the combined ether solution and rinsings with four 65-ml. portions of dilute hydrochloric acid (1 in 100), collecting the aqueous extracts in a 500-ml. volumetric flask. Aerate the combined extracts for 15 to 20 minutes to remove dissolved ether. Dilute to volume with dilute hydrochloric acid (1 in 100), and mix. Filter a portion of the solution through filter paper, discarding the first 25 ml. of the filtrate. Dilute 25.0 ml. of the filtrate to 200.0 ml. with dilute hydrochloric acid (1 in 100), and mix.

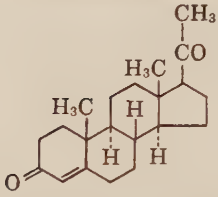
Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* in 1-cm. cells at 254 mμ and at 278 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Record the absorbances of the *Standard preparation* as A_{S254} and A_{S278}, and those of the *Assay preparation* as A_{U254} and A_{U278}. Calculate the quantity, in mg., of $C_{20}H_{24}ClN_3S$ in the portion of the Suppositories taken by the formula $0.617W \times (A_{U254} - A_{U278})/(A_{S254} - A_{S278})$, in which 0.617 is the ratio of the molecular weight of prochlorperazine to that of prochlorperazine maleate, and W is the amount, in mg., of USP Prochlorperazine Maleate Reference Standard weighed out for the *Standard preparation.*

Packaging and storage—Preserve Prochlorperazine Suppositories in tight containers at temperatures below 37°. Do not expose the unwrapped Suppositories to sunlight.

Suppositories available—Prochlorperazine Suppositories usually available contain the following amounts of prochlorperazine: 2.5, 5, and 25 mg.

CATEGORY and DOSE—See Prochlorperazine.

Progesterone



Pregn-4-ene-3,20-dione

$C_{21}H_{30}O_2$ Mol. wt. 314.47

Progesterone contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{30}O_2$, calculated on the dried basis.

Description—Progesterone occurs as a white or creamy white, crystalline powder. It is odorless and is stable in air.

Solubility—Progesterone is practically insoluble in water. It is soluble in alcohol, in acetone, and in dioxane. It is sparingly soluble in vegetable oils.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Progesterone, previously dried in vacuum over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of NF Progesterone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Progesterone in methanol exhibits maxima and minima at the same wavelengths as that of NF Progesterone Reference Standard, similarly measured.

Melting range, *Class Ia,* page 815—Progesterone melts between 128° and 133°. It may also exist in a polymorphic modification, melting at about 121°.

Specific rotation, page 822—The specific rotation of Progesterone, previously dried in vacuum over silica gel for 4 hours, determined in a solution in dioxane containing 200 mg. of Progesterone in each 10 ml., is between +175° and +183°.

Loss on drying, page 814—Dry Progesterone in vacuum over silica gel for 4 hours: it loses not more than 0.5 percent of its weight.

Foreign steroids and other impurities—*Standard preparation*—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Progesterone Reference Standard, previously dried in vacuum over silica gel for 4 hours.

Test preparation—Weigh accurately about 80 mg. of Progesterone, previously dried in vacuum over silica gel for 4 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of chloroform and ethyl acetate (2:1). Use 25.0 ml. of methanol, rather than dehydrated alcohol, to elute the steroid from the silica gel. Determine the absorbance at the maximum at about 241 mμ, and calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Progesterone taken: not more than 3 percent is found.

Assay—Transfer about 200 mg. of Progesterone, accurately weighed, to a 200-ml. volumetric flask, add methanol to volume, and mix. Pipet 5.0 ml. of the solution into a 500-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Progesterone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{21}H_{30}O_2$ in the Progesterone taken by the formula $20C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Progesterone in tight, light-resistant containers.

CATEGORY—Progestin.

USUAL DOSE RANGE—Buccal, **10 mg.** up to four times a day; intramuscular, **2** to **25 mg.**

Progesterone Injection

Progesterone Injection is a sterile solution of progesterone in a suitable solvent. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{30}O_2$.

Identification—The hydrazone obtained in the *Assay* of Progesterone Injection melts between 267° and 275°, page 814.

Other requirements—Progesterone Injection meets the requirements under *Injections*, page 810.

Assay—

Dinitrophenylhydrazine hydrochloride solution—To 500 mg. of 2,4-dinitrophenylhydrazine add 6 ml. of hydrochloric acid, and mix until the hydrazine assumes the characteristic canary-yellow color of the hydrochloride. Add dehydrated alcohol to make 100 ml., and warm the mixture on a steam bath until solution is effected. Allow the solution to cool, and place it in a refrigerator overnight. Filter the solution if necessary. Store in a refrigerator, and use within 3 months.

Procedure—Transfer to a glass-stoppered, 200-ml. conical flask an accurately measured volume of Progesterone Injection, equivalent to between 20 and 25 mg. of progesterone. Add 15 ml. of *n*-hexane, 15 ml. of *Dinitrophenylhydrazine hydrochloride solution*, and 15 ml. of alcohol, and mix. Connect the flask with a reflux condenser, and reflux vigorously for 10 to 15 minutes, swirling the contents of the flask occasionally. Cool, and completely transfer the precipitate to a tared, medium-porosity sintered-glass filter crucible. Rinse the flask with several 5-ml. portions of *n*-hexane, followed by several 5-ml. portions of alcohol, passing the rinsings through the crucible. Remove any crystals of hydrazone adhering to the flask by scrubbing with small portions of alcohol. Wash the precipitate in the crucible first with several 10-ml. portions of *n*-hexane, then with two 5-ml. portions of alcohol, and finally with two 10-ml. portions of *n*-hexane. Dry the precipitate at 105° for 1 hour, cool, and weigh. The weight of the hydrazone so obtained, multiplied by 0.4661, represents the weight of $C_{21}H_{30}O_2$ in the portion of the Injection taken.

Packaging and storage—Preserve Progesterone Injection in single-dose or in multiple-dose containers, preferably of Type I or Type III glass.

Injections available—Progesterone Injection usually available contains the following amounts of progesterone: 5, 10, 25, 50, and 100 mg. in 1 ml.; 50 and 125 mg. in 5 ml.; 100, 250, and 500 mg. in 10 ml.

Category and Dose—See Progesterone.

Sterile Progesterone Suspension

Sterile Progesterone Suspension is a sterile suspension of progesterone in water for injection. It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{21}H_{30}O_2$.

Identification—The progesterone obtained in the *Assay* melts between 127° and 133°, page 814, and meets the requirements of the *Infrared absorption test* under *Progesterone*, page 598.

pH, page 824—The pH of Sterile Progesterone Suspension is between 4.0 and 7.5.

Other requirements—Sterile Progesterone Suspension meets the requirements under *Injections*, page 810.

Assay—Measure accurately a volume of the well-shaken Sterile Progesterone Suspension, equivalent to not less than 100 mg. of progesterone, and filter it through a tared, medium-porosity sintered-glass crucible, previously dried at 105°, re-filtering through the same crucible if not clear. Wash with several 5-ml. portions of water until 2 ml. of the last washing, evaporated on a steam bath, leaves no weighable residue: the weight of the washed solid, dried at 105° to constant weight, represents $C_{21}H_{30}O_2$.

Packaging and storage—Preserve Sterile Progesterone Suspension in single-dose or in multiple-dose containers, preferably of Type I glass.

Suspensions available—Sterile Progesterone Suspension usually available contains the following amounts of progesterone: 10, 25, and 50 mg. in 1 ml.; 250 and 500 mg. in 10 ml.

Category and Dose—See Progesterone.

Progesterone Tablets

Progesterone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{30}O_2$.

Identification—The progesterone obtained in the *Assay* of Progesterone Tablets melts between 126° and 133°, page 814, and meets the requirements of the *Infrared absorption test* under *Progesterone*, page 598.

Disintegration, page 878—Progesterone Tablets meet the requirements as set forth for *Buccal Tablets.*

Content uniformity, *Method II,* page 799—Progesterone Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml. volumetric flask. Add 50 ml. of alcohol, and shake mechanically for 30 minutes. Dilute to volume with alcohol, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with alcohol to provide a solution containing approximately 10 mcg. of progesterone per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Progesterone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity in mg., of $C_{21}H_{30}O_2$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of progesterone, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of progesterone in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

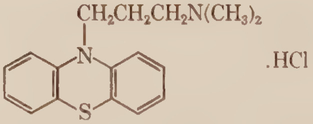
Assay—Weigh and finely powder not less than 20 Progesterone Tablets. Weigh accurately a portion of the powder, equivalent to about 200 mg. of progesterone, triturate it with 50 ml. of acetone, allow the insoluble matter to settle, and decant the supernatant liquid through a filter into a beaker. Repeat this treatment four times with 25-ml. portions of acetone. Completely transfer the insoluble matter to the filter, and wash with several 10-ml. portions of acetone. Evaporate the combined filtrates carefully on a steam bath with the aid of a current of air, and remove the beaker from the bath immediately after evaporation of the acetone. Add slowly, with stirring, 25 ml. of water, and cool the mixture to 10° to 15°. Filter the suspension through a previously dried and tared sintered-glass crucible, and wash the precipitate with several 5-ml. portions of cold water until all traces of color in the residue have been removed. Dry the crucible and contents at 105° to constant weight. The weight of the residue represents the weight of $C_{21}H_{30}O_2$ in the portion of the Tablets taken.

Packaging and storage—Preserve Progesterone Tablets in well-closed containers.

Tablets available—Progesterone Tablets usually available contain the following amounts of progesterone: 10 and 25 mg.

Category and Dose—See Progesterone.

Promazine Hydrochloride*



10-[3-(Dimethylamino)propyl]phenothiazine Monohydrochloride

$C_{17}H_{20}N_2S.HCl$ Mol. wt. 320.89

Promazine Hydrochloride, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{17}H_{20}N_2S.HCl$.

Description—Promazine Hydrochloride occurs as a white to slightly yellow, practically odorless, crystalline powder. It oxidizes upon prolonged exposure to air, and acquires a blue or pink color.

Solubility—Promazine Hydrochloride is freely soluble in water and in chloroform.

Identification—

A: Dissolve 500 mg. of Promazine Hydrochloride in 20 ml. of water, and add 0.5 ml. of nitric acid: an orange precipitate forms which rapidly turns brown. Add an additional 2 ml. of nitric acid, and warm: a yellow solution is produced.

B: Dissolve about 1 g. of Promazine Hydrochloride in 20 ml. of methanol. Add 10 ml. of a boiling 1 in 30 solution of trinitrophenol in methanol, mix, and cool the mixture in an ice bath with constant stirring until bright orange to rust-red crystals appear. Collect the crystals in a medium porosity sintered-glass crucible. Wash the crystals once with 25 ml. of cold methanol, and transfer them to a 50-ml. beaker with the aid of 20 ml. of methanol. Heat on a water bath to dissolve the crystals, and if after heating for a few minutes any undissolved matter is still present, filter while hot through paper. Add 20 ml. of solvent hexane and cool in an ice bath until bright orange to rust-red crystals appear. Collect the crystals on a medium porosity sintered-glass crucible, wash with 10 ml. of cold methanol, followed by 20 ml. of solvent hexane, and dry at 80° for 15 minutes: the picrate so obtained melts between 140° and 147°. (*Caution: Picrates may be explosive.*)

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* Patented. See notice, page ii.

C: Promazine Hydrochloride responds to the test for *Chloride,* page 808, when tested as specified for alkaloidal hydrochlorides.

Melting range, page 814—Promazine Hydrochloride melts within a range of 3° between 172° and 182°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Promazine Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Promazine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—Determine the absorbance of the solution of Promazine Hydrochloride employed for measurement of absorbance in the *Assay* at 301 mμ, using dilute hydrochloric acid (1 in 100) as the blank. Similarly determine the absorbance of a 1 in 10 dilution of this solution, prepared with the same acid, at 251.5 mμ: the ratio 10 ($A_{251.5}/A_{301}$) is between 7.1 and 7.9.

Loss on drying, page 814—Dry Promazine Hydrochloride at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Promazine Hydrochloride yields not more than 0.1 percent of residue on ignition. Retain the residue for the *Heavy metals test.*

Selenium—A *Test Preparation* prepared with 100 mg. of Promazine Hydrochloride and 200 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Heavy metals, page 806—To the residue obtained from Promazine Hydrochloride in the test for *Residue on ignition,* add 2 ml. of hydrochloric acid and 0.5 ml. of nitric acid, and evaporate on a steam bath to dryness. To the residue add 2 ml. of acetic acid T.S. and 15 ml. of water, warm for a few minutes, filter, wash with water to obtain 50 ml. of filtrate, mix well, and use 25 ml. of the filtrate: the heavy metals limit for Promazine Hydrochloride is 50 parts per million.

pH, page 824—The pH of a solution of Promazine Hydrochloride (1 in 20) is between 4.2 and 5.2.

Completeness and clarity of solution—A solution of Promazine Hydrochloride (1 in 10) in water and a solution of Promazine Hydrochloride (1 in 10) in chloroform, are practically clear and show not more than a light yellow color.

Assay—[NOTE: Use low-actinic glassware in this assay.] Transfer about 50 mg. of Promazine Hydrochloride, previously dried at 105° for 2 hours and accurately weighed, to a 1000-ml. volumetric flask, add dilute hydrochloric acid (1 in 100) to volume, and mix. Without delay concomitantly determine the absorbance of this solution and of a solution of NF Promazine Hydrochloride Reference Standard, in the same medium, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 301 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{17}H_{20}N_2S.HCl$ in the portion of Promazine Hydrochloride taken, by the formula $C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Promazine Hydrochloride in tight, light-resistant containers.

CATEGORY—Tranquilizer (major).

USUAL DOSE RANGE—Oral, intramuscular, and intravenous, **10** to **200 mg.,** every 4 to 6 hours.

Promazine Hydrochloride Injection

Promazine Hydrochloride Injection is a sterile solution of promazine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{20}N_2S.HCl$.

Identification—

A: Evaporate a volume of Promazine Hydrochloride Injection, equivalent to about 500 mg. of promazine hydrochloride, with the aid of a current of air, to dryness: the residue responds to *Identification test B* under *Promazine Hydrochloride,* page 600.

B: Determine the absorbance of the solution of Promazine Hydrochloride Injection employed for measurement of absorbance in the *Assay* at 301 mμ, using dilute hydrochloric acid (1 in 100) as the blank. Similarly determine the absorbance of a 1 in 10 dilution of this solution, prepared with the same acid, at 251.5 mμ: the ratio $10(A_{251.5}/A_{301})$ is between 7.1 and 7.9.

pH, page 824—The pH of Promazine Hydrochloride Injection is between 4.0 and 5.5.

Other requirements—Promazine Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—[Note: Use low-actinic glassware in this assay.] Pipet a volume of Promazine Hydrochloride Injection, equivalent to about 50 mg. of promazine hydrochloride, into a 100-ml. volumetric flask, add dilute hydrochloric acid (1 in 100) to volume, and mix. Pipet 10.0 ml. of the solution into a 250-ml. separator, add 20 ml. of water, make alkaline with stronger ammonia water, and extract with four 25-ml. portions of ether. Extract the combined ether extracts with five 15-ml. portions of dilute hydrochloric acid (1 in 100), collecting the aqueous extracts in a 100-ml. volumetric flask. Aerate to remove residual ether, add dilute hydrochloric acid (1 in 100) to volume, and mix. Without delay concomitantly determine the absorbance of this solution and of a solution of NF Promazine Hydrochloride Reference Standard, in the same medium, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 301 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{17}H_{20}N_2S.HCl$ in each ml. of the Injection taken by the formula $(C/V) \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., V is the volume, in ml., of the Injection taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Promazine Hydrochloride Injection in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

Injections available—Promazine Hydrochloride Injection usually available contains the following amounts of promazine hydrochloride: 25 and 50 mg. in 1 ml.; 50 and 100 mg. in 2 ml.; 250 and 500 mg. in 10 ml.

Category and Dose—See Promazine Hydrochloride.

Promazine Hydrochloride Syrup

Promazine Hydrochloride Syrup contains not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{20}N_2S.HCl$.

Identification—Determine the absorbance of the solution of Promazine Hydrochloride Syrup employed for measurement of absorbance in the *Assay* at 301 mμ, using dilute hydrochloric acid (1 in 100) as the blank. Similarly determine the absorbance of a 1 in 10 dilution of this solution, prepared with the same acid, at 251.5 mμ: the ratio $10(A_{251.5}/A_{301})$ is between 7.1 and 7.9.

Assay—[Note: Use low-actinic glassware in this assay.] Pipet a volume of Promazine Hydrochloride Syrup, equivalent to about 10 mg. of promazine hydrochloride, into a 250-ml. separator. Add about 40 ml. of water and 3 ml. of sodium hydroxide solution (1 in 10), mix, and extract the promazine with five 25-ml. portions of ether. Wash the combined ether extracts with 25 ml. of water and discard the aqueous washings. Extract the combined ether extract with one 50-ml. and four 25-ml. portions of dilute hydrochloric acid (1 in 100). Filter the acid extracts through a pledget of cotton washed with dilute hydrochloric acid (1 in 100) into a 250-ml. volumetric flask, add dilute hydrochloric acid (1 in 100) to volume, and mix. Without delay concomitantly determine the absorbance of this solution and of a solution of NF Promazine Hydrochloride Reference Standard, in the same medium, at a concentration of about 40 mcg. per ml., in 1-cm. cells, at the maximum at about 301 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{17}H_{20}N_2S.HCl$ in each ml. of the Syrup taken by the formula $0.25 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., V is the volume, in ml., of the Syrup taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Promazine Hydrochloride Syrup in tight, light-resistant containers.

Syrup available—Promazine Hydrochloride Syrup usually available contains the following amount of promazine hydrochloride: 10 mg. in 5 ml.

Category and Dose—See Promazine Hydrochloride.

Promazine Hydrochloride Tablets

Promazine Hydrochloride Tablets contain not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{17}H_{20}N_2S.HCl$.

Identification—

A: Macerate a portion of finely powdered Promazine Hydrochloride Tablets, equivalent to about 1 g. of promazine hydrochloride, with 20 ml. of methanol. Centrifuge and decant the clear supernatant liquid through filter paper, collecting the filtrate in a 50-ml. beaker: the filtrate responds to *Identification test B* under *Promazine Hydrochloride*, page 600.

B: Determine the absorbance of the solution of Promazine Hydrochloride Tablets employed for measurement of absorbance in the *Assay* at 301 mμ, using dilute hydrochloric acid (1 in 100) as the blank. Similarly determine the absorbance of a 1 in 10 dilution of this solution, prepared with the same acid, at 251.5 mμ: the ratio $10(A_{251.5}/A_{301})$ is between 7.1 and 7.9.

Disintegration time, page 878—The disintegration time limit for Promazine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Promazine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

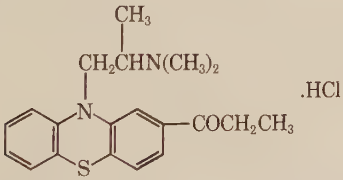
Assay—[Note: Use low-actinic glassware in this assay.] Weigh and finely powder not less than 20 Promazine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of promazine hydrochloride, to a 100-ml. volumetric flask. Add 50 ml. of dilute hydrochloric acid (1 in 100), and shake the mixture mechanically for about one hour. Add dilute hydrochloric acid (1 in 100) to volume, mix, and centrifuge a portion of the mixture. Pipet 10.0 ml. of the clear, supernatant liquid into a 250-ml. separator, and proceed as directed in the *Assay* under *Promazine Hydrochloride Injection*, page 601, beginning with "Add 20 ml. of water . . . ." Calculate the quantity, in mg., of $C_{17}H_{20}N_2S.HCl$ in the portion of the Tablets taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Promazine Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Promazine Hydrochloride Tablets usually available contain the following amounts of promazine hydrochloride: 10, 25, 50, 100, and 200 mg.

Category and Dose—See Promazine Hydrochloride.

Propiomazine Hydrochloride*



±1-[10-[2-(Dimethylamino)propyl]phenothiazin-2-yl]-1-propanone Monohydrochloride

$C_{20}H_{24}N_2OS.HCl$ Mol. wt. 376.95

Propiomazine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{24}N_2OS.HCl$, calculated on the anhydrous basis.

Description—Propiomazine Hydrochloride occurs as a yellow, practically odorless powder.

Solubility—Propiomazine Hydrochloride is very soluble in water, freely soluble in alcohol, and insoluble in benzene.

Identification—Dissolve 500 mg. of Propiomazine Hydrochloride in 15 ml. of chloroform in a 125-ml. separator, add 10 ml. of sodium hydroxide solution (1 in 10), shake well, and filter the chloroform phase through a chloroform-moistened filter paper. Extract the alkaline aqueous phase with two 5-ml. portions of chloroform, wash the filter paper with 5 ml. of chloroform, and evaporate the combined chloroform extracts just to dryness. Dry the residue of propiomazine in a vacuum desiccator to remove the final traces of chloroform. Dissolve the dry propiomazine in 5.0 ml. of a freshly prepared solution of maleic acid in absolute methanol containing 3.20 g. in each 100 ml., and, while heating nearly to boiling on a steam bath, rapidly add 25 ml. of ether with constant stirring. Remove from the steam bath, and continue stirring until crystallization occurs, scratching the sides of the container, if necessary, to induce crystallization. Cool to −5° or lower, and then filter through a medium-porosity sintered-glass filtering crucible. Dry to remove traces of ether, and then reduce the entire residue on the crucible to a fine powder. Dry the powder over phosphorus pentoxide in a desiccator for 24 hours: the propiomazine maleate so obtained melts within a range of 3° between 157° and 165°, page 814.

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* Patented. See notice, page ii.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Propiomazine Hydrochloride, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Propiomazine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Propiomazine Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Propiomazine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance occurring at about 240 mμ, do not differ by more than 3 percent.

pH, page 824—The pH of solution of Propiomazine Hydrochloride (1 in 50) is between 4.6 and 5.6.

Water, page 900—Determine the water content of Propiomazine Hydrochloride by the titrimetric method: not more than 0.5 percent is found.

Residue on ignition, page 858—The residue on ignition from 1 g. of Propiomazine Hydrochloride is negligible.

Assay—

Buffered palladium chloride solution—Warm 500 mg. of palladous chloride with 5 ml. of hydrochloric acid on a steam bath, add 200 ml. of hot water in small increments while stirring, and continue heating until solution is complete. Dilute to 500.0 ml. with water, and mix. Transfer 25.0 ml. of this solution to a 500-ml. volumetric flask, add 50 ml. of 1 *N* sodium acetate and 48 ml. of 1 *N* hydrochloric acid, dilute to volume with water, and mix.

Standard preparation—Transfer about 150 mg. of NF Propiomazine Hydrochloride Reference Standard, accurately weighed, to a 50-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Transfer about 150 mg. of Propiomazine Hydrochloride, accurately weighed, to a 50-ml. volumetric flask, add water to volume, and mix. Transfer 10.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Transfer 3.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate tubes, and transfer 3.0 ml. of water to a third tube to serve as a blank. To each tube add 4.0 ml. of *Buffered palladium chloride solution*, and mix. Concomitantly determine the absorbances of the solutions, in 1-cm. cells at the maximum at about 465 mμ with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{20}H_{24}N_2OS.HCl$ in the Propiomazine Hydrochloride taken by the formula $1.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Propiomazine Hydrochloride in tight containers.

CATEGORY—Sedative.

USUAL DOSE—Intramuscularly or intravenously, **20 mg.**

USUAL DOSE RANGE—**10 mg.** to **40 mg.**

Propiomazine Hydrochloride Injection

Propiomazine Hydrochloride Injection is a sterile solution of propiomazine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{24}N_2OS.HCl$.

NOTE—Do not use the Injection if it is cloudy or contains a precipitate.

Identification—Dilute a volume of Propiomazine Hydrochloride Injection, equivalent to about 10 mg. of propiomazine hydrochloride, to 1000.0 ml. with water, and mix. Determine the absorbance of this solution at 241 mμ and at 273 mμ with a suitable spectrophotometer, using water as the blank: the ratio $10(A_{273}/A_{241})$ is between 6.5 and 6.8.

pH, page 824—The pH of Propiomazine Hydrochloride Injection is between 4.7 and 5.3.

Other requirements—Propiomazine Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—

Buffered palladium chloride solution—Prepare as directed in the *Assay* under *Propiomazine Hydrochloride,* page 603.

Standard preparation—Prepare as directed in the *Assay* under *Propiomazine Hydrochloride,* page 603.

Assay preparation—Transfer to a 50-ml. volumetric flask an accurately measured volume of Propiomazine Hydrochloride Injection, equivalent to about 60 mg. of propiomazine hydrochloride, dilute to volume with water, and mix. Transfer 25.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Propiomazine Hydrochloride,* page 603. Calculate the quantity, in mg., of $C_{20}H_{24}N_2OS.HCl$ in each ml. of the Injection taken by the formula $0.5 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation,* and V is the volume, in ml., of the Injection taken.

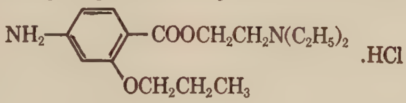
Packaging and storage—Preserve Propiomazine Hydrochloride Injection in single-dose containers, preferably of Type I glass, in a cool place protected from light.

Injections available—Propiomazine Hydrochloride Injection usually available contains the following amounts of propiomazine hydrochloride: 20 mg. in 1 ml.; 40 mg. in 2 ml.

CATEGORY and DOSE—See Propiomazine Hydrochloride.

Propionate, Sodium, page 657

Propoxycaine Hydrochloride*



2-(Diethylamino)ethyl 4-Amino-2-propoxybenzoate Monohydrochloride

$C_{16}H_{26}N_2O_3.HCl$ Mol. wt. 330.86

Propoxycaine Hydrochloride, dried at 105° for 3 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{16}H_{26}N_2O_3.HCl$.

Description—Propoxycaine Hydrochloride occurs as a white, odorless, crystalline solid which discolors on prolonged exposure to light and to air. The pH of a 2 in 100 solution is about 5.4.

Solubility—Propoxycaine Hydrochloride is very soluble in water, slightly soluble in alcohol and in chloroform, and practically insoluble in acetone and in ether.

Identification—

A: A solution of Propoxycaine Hydrochloride (1 in 100) responds to the tests for *Chloride,* page 808.

B: Dissolve about 100 mg. of Propoxycaine Hydrochloride in 10 ml. of diluted hydrochloric acid, cool to 0° in an ice bath, and introduce 5 ml. of a solution of sodium nitrite (1 in 10), stirring gently. Add 2 ml. of a solution of 100 mg. of betanaphthol in 5 ml. of sodium hydroxide T.S. and observe immediately: a bright orange-red precipitate is produced (*presence of a primary aromatic amino group*).

C: Dissolve about 100 mg. of Propoxycaine Hydrochloride in 10 ml. of water, heat almost to boiling, and add, with stirring, 1 ml. of a saturated solution of picric acid in 20 percent alcohol. Cool slowly, collect the precipitate on a filter, wash with a few small portions of water, and dry in a vacuum desiccator over phosphorus pentoxide for 18 hours: the picrate so obtained melts with decomposition between 130° and 138°, page 814. (*Caution: Picrates may be explosive.*)

Melting range, page 814—Propoxycaine Hydrochloride melts between 146° and 151°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Propoxycaine Hydrochloride, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Propoxycaine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Propoxycaine Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Propoxycaine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 303 mμ, do not differ by more than 3 percent.

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* Patented. See notice, page ii.

Loss on drying, page 814—Dry Propoxycaine Hydrochloride at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Propoxycaine Hydrochloride yields not more than 0.2 percent of residue on ignition.

Assay—Dissolve about 500 mg. of Propoxycaine Hydrochloride, previously dried at 105° for 3 hours and accurately weighed, in 200 ml. of ice-cold water containing 1 g. of potassium bromide and 2.5 ml. of hydrochloric acid, and titrate with 0.1 *M* sodium nitrite, determining the endpoint by spotting the reaction solution on starch iodide paper. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 33.09 mg. of $C_{16}H_{26}N_2O_3 . HCl$.

Packaging and storage—Preserve Propoxycaine Hydrochloride in well-closed, light-resistant containers.

CATEGORY—Local anesthetic.

Propoxycaine Hydrochloride Injection

Propoxycaine Hydrochloride Injection is a sterile solution of propoxycaine hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{16}H_{26}N_2O_3 . HCl$.

Identification—Propoxycaine Hydrochloride Injection responds to *Identification tests B* and *C* under *Propoxycaine Hydrochloride,* page 605.

Other requirements—Propoxycaine Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—Transfer an accurately measured volume of Propoxycaine Hydrochloride Injection, equivalent to about 10 mg. of propoxycaine hydrochloride, to a small separator, add 10.0 ml. of chloroform and 3 ml. of ammonia T.S., stopper the separator immediately, and shake vigorously for 1 minute. Allow the layers to separate for 1 minute, then remove the bulk of the chloroform layer carefully to exclude any contamination by the aqueous phase. Transfer 5.0 ml. of the chloroform solution to a second small separator, add 10.0 ml. of about 2 *N* hydrochloric acid, stopper the separator immediately, and shake vigorously for 1 minute. Allow the layers to separate for 1 minute, then withdraw the chloroform layer completely, discard the chloroform, and briefly centrifuge the aqueous phase. Transfer 2.0 ml. of the clear, supernatant liquid to a 100-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Propoxycaine Hydrochloride Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 303 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{16}H_{26}N_2O_3 . HCl$ in each ml. of the Injection taken by the formula $(C/V) \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., V is the volume, in ml., of the Injection taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Propoxycaine Hydrochloride Injection in single-dose or multiple-dose containers.

Injections available—Propoxycaine Hydrochloride Injection usually available contains the following amount of propoxycaine hydrochloride: 150 mg. in 30 ml.

CATEGORY—See Propoxycaine Hydrochloride.

Propoxycaine and Procaine Hydrochlorides and Levarterenol Bitartrate Injection, page 590

Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection, page 591

Propoxyphene Hydrochloride and Aspirin Capsules

Propoxyphene Hydrochloride and Aspirin Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_{22}H_{29}NO_2 . HCl$ (propoxyphene hydrochloride) and of $C_9H_8O_4$ (aspirin).

Identification—

A: The infrared absorption spectrum of the *Assay preparation*, prepared as directed in the *Assay for propoxyphene hydrochloride*, exhibits maxima only at the same wavelengths as that of the *Standard preparation*, prepared as directed in the *Assay for propoxyphene hydrochloride*.

B: Boil the contents of one or more Propoxyphene Hydrochloride and Aspirin Capsules with 5 ml. of sodium hydroxide T.S. for a few minutes, cool, filter, and add 10 ml. of diluted sulfuric acid to the filtrate: a white precipitate of salicylic acid is formed. Filter, and divide the filtrate into two parts. To one part of the filtrate add 1 ml. of alcohol and 1 ml. of sulfuric acid, and warm: the odor of ethyl acetate is perceptible. To the other portion of the filtrate add 1 or 2 drops of ferric chloride T.S., mix, and neutralize with ammonia T.S.: a violet to purple color is produced (*presence of aspirin*).

Weight variation, page 901—Propoxyphene Hydrochloride and Aspirin Capsules meet the requirements of the weight variation test for capsules.

Free salicylic acid—

Ferric chloride-urea reagent—Dissolve by swirling, without the aid of heat, 60 g. of urea in a mixture of 8 ml. of ferric chloride solution (6 in 10) and 42 ml. of 0.05 *N* hydrochloric acid. Adjust the resulting solution to a pH of 3.2, if necessary, by the addition of 6 *N* hydrochloric acid.

Standard preparation—Transfer 30.0 mg. of salicylic acid, previously dried over silica gel for 3 hours and accurately weighed, to a 100-ml. volumetric flask, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a 50-ml. volumetric flask containing 10 ml. of methanol, 2 drops of hydrochloric acid, and 10 ml. of a 1 in 10 solution of glacial acetic acid in ether, dilute to volume with chloroform, and mix.

Test preparation—Pack a pledget of glass wool in the base of a 25 × 200-mm. chromatographic tube, and uniformly pack the tube with a mixture of 3 g. of chromatographic siliceous earth and 2 ml. of freshly prepared *Ferric chloride-urea reagent*. Weigh accurately an amount of the contents of Propoxyphene Hydrochloride and Aspirin Capsules, equivalent to 100 mg. of aspirin, mix with 10 ml. of chloroform by stirring for 3 minutes, and then transfer to the chromatographic column with the aid of a few ml. of chloroform. Pass 50 ml. of chloroform through the column, rinse the tip of the chromatographic tube with chloroform, and discard the eluate. Prepare as a receiver a 50-ml. volumetric flask containing 10 ml. of methanol and 2 drops of hydrochloric acid, and elute any salicylic acid from the column by passing 10 ml. of a 1 in 10 solution of glacial acetic acid in ether that has been recently saturated with water, followed by 30 ml of chloroform. Dilute the eluate to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 306 mμ, with a suitable spectrophotometer, using as the blank a solvent mixture of the same composition as that used for the *Standard preparation:* the absorbance of the *Test preparation* does not exceed that of the *Standard preparation* (3.0 percent, calculated on the labeled aspirin content).

Assay for propoxyphene hydrochloride—

Standard preparation—Transfer about 130 mg. of USP Propoxyphene Hydrochloride Reference Standard, accurately weighed, to a 125-ml. separator containing 25 ml. of water, add 0.4 ml. of sodium hydroxide solution (1 in 2), and continue as directed under *Assay preparation*, beginning with "Add 50 ml. of chloroform. . . ."

Assay preparation—Remove as completely as possible the contents of not less than 20 Propoxyphene Hydrochloride and Aspirin Capsules, and weigh accurately. Transfer an accurately weighed portion of the powder, equivalent to about 130 mg. of propoxyphene hydrochloride, to a 125-ml. separator, add 25 ml. of water, heat on a steam bath for 5 minutes, and cool. Crush any remaining solids with the blunt end of a glass rod, and add 2 ml. of sodium hydroxide solution (1 in 2) while swirling. Add 50 ml. of chloroform, stopper, and gently extract the suspension for at least 3 minutes. Allow the two liquid layers to separate, and filter the chloroform phase through a layer of anhydrous sodium sulfate into a 250-ml. beaker. Extract the aqueous phase with three 50-ml. portions of chloroform, filtering each extract through the anhydrous sodium sulfate into the same 250-ml. beaker. (Retain the water layer for the determination of aspirin.) Evaporate the combined chloroform extracts in the beaker to about 25 ml., then quantitatively transfer to a 50-ml. volumetric flask with the aid of chloroform, dilute to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbance of the *Standard preparation* and of the *Assay preparation*, in 1-mm. cells, at the maximum at about 5.80 μ, with a suitable infrared spectrophotometer, using chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{29}NO_2.HCl$ in the portion of the Capsules taken by the formula $50C \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*.

Assay for aspirin—

Standard preparation—Transfer to a 150-ml. beaker about 650 mg. of USP Aspirin Reference Standard, accurately weighed, add 50 ml. of water and 6 ml. of sodium hydroxide solution (1 in 2), mix, and continue as directed under *Assay preparation,* beginning with "... cover with a watch glass, and heat on a steam bath for 15 minutes."

Assay preparation—Transfer to a 150-ml. beaker the water layer retained from the *Assay preparation* in the *Assay for propoxyphene hydrochloride,* add 2 ml. of sodium hydroxide solution (1 in 2), cover with a watch glass, and heat on a steam bath for 15 minutes. Allow the solution to cool slowly, and acidify with dilute sulfuric acid solution (1 in 2) by carefully pouring the acid down the lip of the beaker while the watch glass remains in place. Again allow the contents of the beaker to cool. Quantitatively transfer the contents of the beaker to a 250-ml. separator with the aid of water and chloroform, add 50 ml. of chloroform, stopper, and gently extract the suspension for at least 3 minutes. Allow the two liquid layers to separate. Filter the chloroform phase through a layer of anhydrous sodium sulfate into a 250-ml. beaker. Extract the aqueous phase with three 50-ml. portions of chloroform, filtering each extract through the anhydrous sodium sulfate into the same 250-ml. beaker. Evaporate the combined chloroform extracts in the beaker to about 25 ml., quantitatively transfer to a 50-ml. volumetric flask with the aid of chloroform, dilute to volume with chloroform, and mix.

Procedure—Concomitantly determine the absorbance of the *Standard preparation* and of the *Assay preparation,* in 0.1-mm. cells, at the maximum at about 6.02 μ, with a suitable infrared spectrophotometer, using chloroform as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_9H_8O_4$ in the portion of the Capsules taken by the formula $50C \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation.*

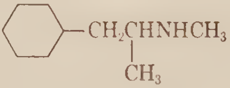
Packaging and storage—Preserve Propoxyphene Hydrochloride and Aspirin Capsules in well-closed containers.

Capsules available—Propoxyphene Hydrochloride and Aspirin Capsules usually available contain the following amount of propoxyphene hydrochloride: 65 mg.; and of aspirin: 325 mg.

CATEGORY—Analgesic.

USUAL DOSE FOR ASPIRIN—**325 mg.** every 4 hours: FOR PROPOXYPHENE HYDROCHLORIDE—**65 mg.** three or four times a day.

Propylhexedrine



N,α-Dimethylcyclohexaneethylamine

$C_{10}H_{21}N$ Mol. wt. 155.29

Propylhexedrine contains not less than 98.0 percent and not more than 101.0 percent of $C_{10}H_{21}N$.

Description—Propylhexedrine is a clear, colorless liquid, having a characteristic, amine-like odor. It volatilizes slowly at room temperature. It absorbs carbon dioxide from the air, and its solutions are alkaline to litmus. It boils at about 205°.

Solubility—Propylhexedrine is very slightly soluble in water. It is miscible with alcohol, with chloroform, and with ether.

Identification—

A: To 3 ml. of water contained in a small flask add about 0.1 ml. of Propylhexedrine and 0.5 ml. of 1 *N* hydrochloric acid, and agitate the mixture until clear. Add 20 ml. of trinitrophenol T.S., stopper the flask, shake vigorously for a few minutes, and allow to stand for 2 hours. Filter, wash the precipitate with about 20 ml. of cold water, and dry in vacuum at 60° for 4 hours: the picrate so obtained melts between 108° and 110°, page 814. (*Caution: Picrates may be explosive.*)

B: A solution, prepared as directed in *Identification test A,* yields a brown precipitate with iodine T.S., and a white precipitate with mercuric-potassium iodide T.S.

Specific gravity, page 866—The specific gravity of Propylhexedrine is not less than 0.848 and not more than 0.852.

Assay—Tare a glass-stoppered conical flask containing about 15 ml. of water, add quickly about 0.5 ml. of Propylhexedrine, and reweigh. Add to the contents of the flask 30 ml. of neutralized alcohol, then add 3 drops of methyl red T.S., and titrate with 0.1 *N* sulfuric acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sulfuric acid is equivalent to 15.53 mg. of $C_{10}H_{21}N$.

Packaging and storage—Preserve Propylhexedrine in tight containers.

Category—Adrenergic (vasoconstrictor).

Application—By inhalation as required.

Propylhexedrine Inhalant

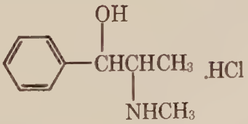
Propylhexedrine Inhalant consists of cylindrical rolls of suitable fibrous material impregnated with propylhexedrine, usually aromatized, and contained in a suitable inhaler. The inhaler contains not less than 90.0 percent and not more than 125.0 percent of the labeled amount of $C_{10}H_{21}N$.

Identification—Place the contents of one inhaler of Propylhexedrine Inhalant in a glass-stoppered flask, add 50 ml. of methanol, and allow to stand for 1 hour with frequent agitation. Filter, pressing out the roll on the filter. Add to the filtrate 1 *N* hydrochloric acid until it is slightly acid to moistened litmus paper, then add 30 ml. of water, and evaporate to about 20 ml. Cool, transfer to a small separator, and shake with 10 ml. of ether. Withdraw the water layer, warm it on a steam bath to expel any ether, and dilute to about 25 ml. From 10 ml. of the solution, precipitate the propylhexedrine with trinitrophenol T.S. as directed in *Identification test A* under *Propylhexedrine*, page 608: the propylhexedrine picrate so obtained melts between 108° and 110°, page 814. (*Caution: Picrates may be explosive.*)

Assay—Place the contents of 2 inhalers of Propylhexedrine Inhalant in the thimble of a continuous extraction apparatus, and quickly assemble the apparatus. Rinse each of the emptied inhalers with about 20 ml. of methanol, pouring the rinsings through the condenser into the extraction flask. Add through the condenser 20 to 30 ml. of methanol, and extract for 15 to 20 cycles. Cool the extract, transfer it completely with the aid of small portions of methanol to a 100-ml. volumetric flask, dilute with methanol to volume, and mix. To 50.0 ml. of the solution add 25.0 ml. of 0.1 *N* sulfuric acid, and evaporate to about 40 ml. Cool, add 3 drops of methyl red T.S., and titrate the excess acid with 0.1 *N* sodium hydroxide. Each ml. of 0.1 *N* sulfuric acid is equivalent to 15.53 mg. of $C_{10}H_{21}N$.

Category and Application—See Propylhexedrine.

Pseudoephedrine Hydrochloride



(+)-*threo*-α[-(1-Methylamino)ethyl]benzyl Alcohol Hydrochloride

$C_{10}H_{15}NO . HCl$ Mol. wt. 201.70

Pseudoephedrine Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{10}H_{15}NO . HCl$, calculated on the dried basis.

Description—Pseudoephedrine Hydrochloride occurs as fine white to off-white crystals or as a powder having a faint characteristic odor. Its solutions are neutral to litmus paper.

Solubility—Pseudoephedrine Hydrochloride is soluble in water, in alcohol, and in chloroform.

Identification—

A: To 1 ml. of a solution of Pseudoephedrine Hydrochloride (1 in 100) add 0.1 ml. of cupric sulfate T.S., followed by 1 ml. of sodium hydroxide solution (1 in 5): a reddish purple color develops. To the mixture add 1 ml. of ether, and shake well: the ether layer becomes purple and the aqueous layer blue.

B: A solution of Pseudoephedrine Hydrochloride responds to the test for *Chloride*, page 808.

Melting range, page 814—Pseudoephedrine Hydrochloride melts between 181° and 186°.

Infrared absorption, page 866—The

infrared absorption spectrum of a potassium bromide dispersion of Pseudoephedrine Hydrochloride, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Pseudoephedrine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2000 solution of Pseudoephedrine Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Pseudoephedrine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 257 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Pseudoephedrine Hydrochloride, previously dried at 105° for 3 hours, determined in a solution containing 1 g. in each 10 ml., is between +59° and +62°.

Loss on drying, page 814—Dry Pseudoephedrine Hydrochloride at 105° for 3 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Pseudoephedrine Hydrochloride yields not more than 0.1 percent residue on ignition.

Sulfate—Dissolve 50 mg. of Pseudoephedrine Hydrochloride in 40 ml. of water, and add 1 ml. of diluted hydrochloric acid and 1 ml. of barium chloride T.S.: no turbidity develops within 10 minutes.

Assay—Dissolve about 400 mg. of Pseudoephedrine Hydrochloride, accurately weighed, in a mixture of 50 ml. of glacial acetic acid and 10 ml. of mercuric acetate T.S., add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid, to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 20.17 mg. of $C_{10}H_{15}NO.HCl$.

Packaging and storage—Preserve Pseudoephedrine Hydrochloride in tight, light-resistant containers.

CATEGORY—Adrenergic.

USUAL DOSE—**30 mg.** three times a day.

USUAL DOSE RANGE—**30** to **60 mg.** three or four times a day.

Pseudoephedrine Hydrochloride Syrup

Pseudoephedrine Hydrochloride Syrup contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{10}H_{15}NO.HCl$.

Identification—

A: To a volume of Pseudoephedrine Hydrochloride Syrup, equivalent to about 60 mg. of pseudoephedrine hydrochloride, add sodium hydroxide T.S. to produce a pH of about 11, extract with about 15 ml. of ether, filter, and evaporate the filtrate to dryness on a steam bath: the residue, dissolved in a mixture of 5 ml. of water and 2 drops of diluted hydrochloric acid, responds to *Identification test A* under *Pseudoephedrine Hydrochloride*, page 609.

B: Extract a volume of Pseudoephedrine Hydrochloride Syrup, equivalent to about 120 mg. of pseudoephedrine hydrochloride, with two 30-ml. portions of ether, discard the extracts, and add 4 ml. of sodium hydroxide T.S. Extract with 30 ml. of chloroform, evaporate the chloroform on a steam bath, avoiding overheating: the pseudoephedrine so obtained melts at about 118°, page 814.

Reaction—Pseudoephedrine Hydrochloride Syrup is acid to litmus.

Assay—Transfer an accurately measured volume of Pseudoephedrine Hydrochloride Syrup, equivalent to about 300 mg. of pseudoephedrine hydrochloride, to a 125-ml. separator, add 10 ml. of sodium hydroxide T.S., and extract with three 20-ml. portions of chloroform. Shake the combined extracts with 10 ml. of water in another separator, collect the washings in another separator, and filter the chloroform through a pledget of cotton into a 250-ml. beaker. Shake the wash water with two 10-ml. portions of chloroform, and add the chloroform to the chloroform filtrate. To the combined chloroform solutions add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 20.17 mg. of $C_{10}H_{15}NO.HCl$.

Packaging and storage—Preserve Pseudoephedrine Hydrochloride Syrup in tight, light-resistant containers.

Syrup available—Pseudoephedrine Hydrochloride Syrup usually available contains the following amount of pseudoephedrine hydrochloride: 30 mg. in 5 ml.

CATEGORY and DOSE—See Pseudoephedrine Hydrochloride.

Pseudoephedrine Hydrochloride Tablets

Pseudoephedrine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{10}H_{15}NO.HCl$.

Identification—

A: A mixture of powdered Pseudoephedrine Hydrochloride Tablets, equivalent to about 10 mg. of pseudoephedrine hydrochloride, and 1 ml. of water responds to *Identification test A* under *Pseudoephedrine Hydrochloride*, page 609.

B: Triturate a number of Pseudoephedrine Hydrochloride Tablets, equivalent to about 180 mg. of pseudoephedrine hydrochloride, with chloroform, filter through paper backed by a pledget of cotton, and evaporate the chloroform on a steam bath, avoiding overheating. Recrystallize the residue from a small amount of dehydrated alcohol: the pseudoephedrine hydrochloride so obtained melts between 180° and 186°, page 814.

Disintegration, page 878—The disintegration time limit for Pseudoephedrine Hydrochloride Tablets is 15 minutes.

Content uniformity, *Method I*, page 799—Pseudoephedrine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Pseudoephedrine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 30 mg. of pseudoephedrine hydrochloride, to the distilling flask of a microsteam-distilling apparatus, add 1 g. of sodium chloride, 1.5 ml. of water, and 4 ml. of sodium hydroxide solution (1 in 2), and steam distil for 6 minutes. Collect a minimum of 20 ml. of distillate in a 50-ml. volumetric flask containing 10.0 ml. of 0.5 N hydrochloric acid, with the tip of the delivery tube positioned beneath the surface of the liquid. Dilute to volume with water, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Pseudoephedrine Hydrochloride Reference Standard, in 0.1 N hydrochloric acid at a concentration of about 600 mcg. per ml., in 1-cm. cells, at the maximum at about 257 mμ, with a suitable spectrophotometer, using 0.1 N hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{10}H_{15}NO.HCl$ in the portion of Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Pseudoephedrine Hydrochloride Tablets in tight containers.

Tablets available—Pseudoephedrine Hydrochloride Tablets usually available contain the following amounts of pseudoephedrine hydrochloride: 30 and 60 mg.

CATEGORY and DOSE—See Pseudoephedrine Hydrochloride.

Pumice

Pumice is a substance of volcanic origin, consisting chiefly of complex silicates of aluminum, potassium, and sodium.

Description—Pumice occurs as very light, hard, rough, porous, grayish masses, or as a gritty grayish powder. It is odorless and tasteless, and is stable in air.

Solubility—Pumice is practically insoluble in water and is not attacked by acids.

Powdered Pumice—Powdered Pumice meets the following requirements:

"Pumice Flour" or "Superfine Pumice": not less than 97 percent of pumice flour or superfine pumice passes through a No. 200 standard mesh sieve.

"Fine Pumice": not less than 95 percent of fine pumice passes through a No. 150 standard mesh sieve, and not more than 75 percent passes through a No. 200 standard mesh sieve.

"Coarse Pumice": not less than 95 percent of coarse pumice passes through a No. 60 standard mesh sieve and not more than 5 percent passes through a No. 200 standard mesh sieve.

Water-soluble substances—Boil 10 g. of Pumice with 50 ml. of water for 30 minutes, adding water from time to time to maintain approximately the original volume, and then filter: the filtrate is neutral to litmus, and one-half of this filtrate, when evaporated and dried at 105° for 1 hour, yields not more than 10 mg. of residue.

Acid-soluble substances—Boil 1 g. of Pumice with 25 ml. of diluted hydrochloric acid for 30 minutes, adding water from time to time to maintain approximately the original volume, and then filter the liquid. Add 5 drops of sulfuric acid to the filtrate, evaporate to dryness, ignite, and weigh the residue: not more than 60 mg. of residue is obtained.

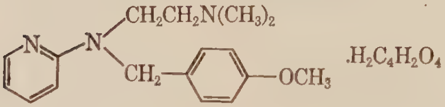
Iron—Acidify the remaining half of the filtrate from the test for *Water-soluble substances* with hydrochloric acid, and add a few drops of potassium ferrocyanide T.S.: no blue color is produced.

Packaging and storage—Preserve Pumice in well-closed containers.

Labeling—Label powdered Pumice to indicate, in descriptive terms, the fineness of the powder.

CATEGORY—Abrasive (dental).

Pyrilamine Maleate



2-[[2-(Dimethylamino)ethyl](*p*-methoxybenzyl)amino]pyridine Maleate (1:1)

$C_{17}H_{23}N_3O . C_4H_4O_4$ Mol. wt. 401.47

Pyrilamine Maleate, dried in vacuum over phosphorus pentoxide for 5 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{17}H_{23}N_3O . C_4H_4O_4$.

Description—Pyrilamine Maleate occurs as a white, crystalline powder, usually having a faint odor. Its solutions are acid to litmus.

Solubility—Pyrilamine Maleate is very soluble in water, and is freely soluble in alcohol and chloroform. Pyrilamine Maleate is slightly soluble in ether and in benzene.

Identification—

A: Dissolve 25 mg. of Pyrilamine Maleate in 5 ml. of sulfuric acid: a cherry-red color is produced. Dilute the solution with 20 ml. of water: the color disappears, leaving a turbid solution from which a white or cream-colored precipitate separates in a few minutes.

B: Dissolve about 200 mg. of Pyrilamine Maleate in 5 ml. of diluted sulfuric acid, and extract the solution with two 50-ml. portions of ether. Wash the combined ether extracts with two 2-ml. portions of water, and evaporate the ether: the white, crystalline residue of maleic acid so obtained melts within a 3° range between 131° and 137°, page 814.

Melting range, page 814—Pyrilamine Maleate melts between 99° and 103°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Pyrilamine Maleate, previously dried in vacuum over phosphorus pentoxide for 5 hours, exhibits maxima only at the same wavelengths as that of NF Pyrilamine Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Pyrilamine Maleate in 0.5 *N* sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Pyrilamine Maleate Reference Standard, similarly measured, and the respective absorptivities calculated on the dried basis, at the points of maximum absorbance, occurring at about 236 mμ and 312 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Pyrilamine Maleate in vacuum over phosphorus pentoxide for 5 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Pyrilamine Maleate yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 400 mg. of Pyrilamine Maleate, previously dried in vacuum over phosphorus pentoxide for 5 hours and accurately weighed, in 50 ml. of glacial acetic acid. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 20.07 mg. of $C_{17}H_{23}N_3O . C_4H_4O_4$.

Packaging and storage—Preserve Pyrilamine Maleate in tight, light-resistant containers.

CATEGORY—Antihistaminic.

USUAL DOSE—**25 mg.** up to four times a day.

USUAL DOSE RANGE—**25** to **50 mg.**

Pyrilamine Maleate Tablets

Pyrilamine Maleate Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{17}H_{23}N_3O.C_4H_4O_4$.

Identification—

A: Extract a quantity of finely powdered Pyrilamine Maleate Tablets, equivalent to about 300 mg. of pyrilamine maleate, with three 5-ml. portions of chloroform. Filter the combined chloroform extracts, and evaporate to dryness: a portion of approximately 25 mg. of the residue so obtained responds to *Identification test A* under *Pyrilamine Maleate*, page 612.

B: The remainder of the residue obtained in the preceding test responds to *Identification test B* under *Pyrilamine Maleate*, page 612, the solution in diluted sulfuric acid being filtered prior to extraction with ether.

C: Pyrilamine Maleate Tablets meet the requirements under *Identification—Organic Nitrogenous Bases*, page 810.

Disintegration, page 878—The disintegration time limit for Pyrilamine Maleate Tablets is 30 minutes.

Content Uniformity, *Method I*, page 799—Pyrilamine Maleate Tablets meet the requirements of the content uniformity test for tablets.

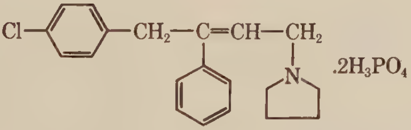
Assay—Proceed with Pyrilamine Maleate Tablets as directed under *Salts of Organic Nitrogenous Bases*, page 865, determining the absorbance at the maximum at about 315 mμ. Calculate the quantity, in mg., of $C_{17}H_{23}N_3O.C_4H_4O_4$ in the portion of the Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., calculated on the dried basis, of NF Pyrilamine Maleate Reference Standard in the *Standard preparation*.

Packaging and storage—Preserve Pyrilamine Maleate Tablets in well-closed containers.

Tablets available—Pyrilamine Maleate Tablets usually available contain the following amounts of pyrilamine maleate: 25 and 50 mg.

CATEGORY and DOSE—See Pyrilamine Maleate.

Pyrrobutamine Phosphate*



1-[γ-(p-Chlorobenzyl)cinnamyl]pyrrolidine Phosphate (1:2)

$C_{20}H_{22}ClN.2H_3PO_4$ Mol. wt. 507.85

Pyrrobutamine Phosphate contains not less than 98.0 percent and not more than 101.0 percent of $C_{20}H_{22}ClN.2H_3PO_4$, calculated on the dried basis.

Description—Pyrrobutamine Phosphate occurs as a white, or almost white, crystalline powder, usually having a faint odor.

Solubility—Pyrrobutamine Phosphate is soluble in water and slightly soluble in alcohol. It is practically insoluble in chloroform and in ether.

Identification—

A: Dissolve 20 mg. of Pyrrobutamine Phosphate in 10 ml. of water, make alkaline with ammonia T.S., and extract the pyrrobutamine base with 10 ml. of ether. Evaporate the ether extract on a steam bath to dryness with the aid of a current of air. To the residue add 5 ml. of a 1 in 50 solution of citric acid in acetic anhydride, and warm the mixture on a steam bath: the solution acquires a dark red to purple color.

B: Pyrrobutamine Phosphate responds to the tests for *Phosphate*, page 809.

Melting range, page 814—Pyrrobutamine Phosphate melts between 127° and 131°.

C: Pyrrobutamine Phosphate meets the requirements under *Identification—Organic Nitrogenous Bases*, page 810, using chloroform, rather than carbon disulfide, as the solvent and determining the infrared absorption between 2 μ and 15 μ, in a 0.1-mm. cell.

Ultraviolet absorption, page 866—The

ultraviolet absorption spectrum of a 1 in 100,000 solution of Pyrrobutamine Phosphate in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Pyrrobutamine Phosphate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 226 mμ, do not differ by more than 3 percent.

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* Patented. See notice, page ii.

Loss on drying, page 814—Dry Pyrrobutamine Phosphate at 105° for 3 hours: it loses not more than 1 percent of its weight.

Heavy metals, page 806—Transfer 1.0 g. of Pyrrobutamine Phosphate to a platinum crucible and ignite until the residue is free from carbon. Cool, moisten the residue with 1 ml. of hydrochloric acid, and evaporate to dryness on a steam bath. Add 2 ml. of diluted acetic acid, digest on a steam bath for 5 minutes, filter, and wash the residue with sufficient water to make 25 ml.: the heavy metals limit for Pyrrobutamine Phosphate is 20 parts per million.

Assay—Accurately weigh about 1 g. of Pyrrobutamine Phosphate, and transfer quantitatively to a 125-ml. conical flask containing about 75 ml. of glacial acetic acid. Add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 50.78 mg. of $C_{20}H_{22}ClN.2H_3PO_4$.

Packaging and storage—Preserve Pyrrobutamine Phosphate in tight, light-resistant containers.

CATEGORY—Antihistaminic.
USUAL DOSE—**15 mg.** three times a day.
USUAL DOSE RANGE—**15** to **30 mg.**

Pyrrobutamine Phosphate Tablets

Pyrrobutamine Phosphate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{20}H_{22}ClN.2H_3PO_4$.

Identification—

A: Dissolve a quantity of finely powdered Pyrrobutamine Phosphate Tablets, equivalent to about 75 mg. of pyrrobutamine phosphate, in 50 ml. of water, mix, and filter. The filtrate responds to the tests for *Phosphate,* page 809.

B: The solution prepared from Pyrrobutamine Phosphate Tablets in the *Assay* exhibits an absorbance maximum at 226 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Pyrrobutamine Phosphate Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Pyrrobutamine Phosphate Tablets meet the requirements of the content uniformity test for tablets.

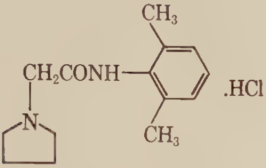
Assay—Weigh and finely powder not less than 20 Pyrrobutamine Phosphate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 30 mg. of pyrrobutamine phosphate, to a 100-ml. volumetric flask, add 50 ml. of water, allow to stand for 30 minutes with frequent agitation, dilute to volume, mix, and filter, rejecting the first 20 ml. of filtrate. Transfer 5.0 ml. of the subsequent filtrate to a 125-ml. separator, make distinctly alkaline to litmus with sodium hydroxide T.S., and extract with six 20-ml. portions of ether, collecting the ether extracts in a 250-ml. separator. Wash the combined ether extracts with 10 ml. of water, and discard the water. Extract the ether solution with four 20-ml. portions of 1 *N* phosphoric acid, collecting the acid extracts in a 100-ml. volumetric flask, dilute to volume with the acid, and mix. Concomitantly determine the absorbance of this solution, and of a solution of NF Pyrrobutamine Phosphate Reference Standard, in 1 *N* phosphoric acid, at a concentration of about 15 mcg. per ml., in 1-cm. cells, at the maximum at about 226 mμ, with a suitable spectrophotometer, using 1 *N* phosphoric acid as the blank. Calculate the quantity, in mg., of $C_{20}H_{22}ClN.2H_3PO_4$ in the portion of the Tablets taken, by the formula $2C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Pyrrobutamine Phosphate Tablets in tight, light-resistant containers.

Tablets available—Pyrrobutamine Phosphate Tablets usually available contain the following amount of pyrrobutamine phosphate: 15 mg.

CATEGORY and DOSE—Dee Pyrrobutamine Phosphate.

Pyrrocaine Hydrochloride*



1-Pyrrolidineaceto-2′,6′-xylidide Hydrochloride

$C_{14}H_{20}N_2O.HCl$ Mol. wt. 268.79

Pyrrocaine Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{14}H_{20}N_2O.HCl$, calculated on the dried basis.

Description—Pyrrocaine Hydrochloride occurs as a white, odorless, crystalline powder.

Solubility—Pyrrocaine Hydrochloride is soluble in water, in alcohol, and in isopropanol. It is practically insoluble in chloroform and in ether.

Identification—

A: A 1 in 20 solution of Pyrrocaine Hydrochloride yields a brown precipitate with iodine T.S., and a white precipitate with mercuric-potassium iodide T.S.

B: A 1 in 100 solution of Pyrrocaine Hydrochloride responds to the tests for *Chloride*, page 808.

Melting range, page 814—Pyrrocaine Hydrochloride melts between 200° and 204°.

Loss on drying, page 814—Dry Pyrrocaine Hydrochloride at 105° for 2 hours: it loses not more than 1 percent of its weight.

Assay—Dissolve about 500 mg. of Pyrrocaine Hydrochloride, accurately weighed, in 50 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in dioxane to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 26.88 mg. of $C_{14}H_{20}N_2O.HCl$.

CATEGORY—Local anesthetic (dental).

USUAL DOSE—Infiltration, **1 ml.** of a 2 percent solution; nerve block, **1.5** to **2 ml.** of a 2 percent solution.

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* Patented. See notice, page ii.

Pyrrocaine Hydrochloride and Epinephrine Injection

Pyrrocaine Hydrochloride and Epinephrine Injection is a sterile solution of pyrrocaine hydrochloride and epinephrine in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{14}H_{20}N_2O.HCl$ (pyrrocaine hydrochloride), and not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3$ (epinephrine).

Identification—

A: Heat 5 ml. of Pyrrocaine Hydrochloride and Epinephrine Injection with 15 ml. of alcohol and 2 ml. of a hot saturated solution of picric acid in alcohol, and cool. Filter, recrystallize the precipitate from alcohol, and dry the crystals in vacuum for 6 hours: the picrate so obtained melts between 216° and 218°. (*Caution: Picrates may be explosive.*)

B: Pyrrocaine Hydrochloride and Epinephrine Injection responds to the test for *Chloride*, page 808.

pH, page 824—The pH of Pyrrocaine Hydrochloride and Epinephrine Injection is between 3.5 and 5.0.

Other requirements—Pyrrocaine Hydrochloride and Epinephrine Injection meets the requirements under *Injections*, page 810.

Assay for pyrrocaine hydrochloride—Transfer an accurately measured volume of Pyrrocaine Hydrochloride and Epinephrine Injection, equivalent to about 500 mg. of pyrrocaine hydrochloride, to a 125-ml. separator, add 2 ml. of sodium hydroxide T.S., and extract with four 25-ml. portions of chloroform. Filter the chloroform extracts into a 125-ml. conical flask, wash the filter with chloroform, and evaporate the combined filtrate and washings almost to dryness on a steam bath with the aid of a stream of warm air. Add 40.0 ml. of 0.1 *N* sulfuric acid to the residue, heat on a steam bath until the odor of chloroform is no longer perceptible, and cool. Add 2 drops of indicator consisting of a mixture of 3 parts of bromocresol blue T.S. and 1 part of methyl red T.S., and titrate with 0.1 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sulfuric acid is equivalent to 26.88 mg. of $C_{14}H_{20}N_2O.HCl$.

Assay for epinephrine—

Ferro-citrate Solution and *Buffer Solution*—Prepare as directed under *Epinephrine Assay*, page 803.

Standard preparation—Transfer about 36 mg. of USP Epinephrine Bitartrate Reference Standard, previously dried in vacuum over silica gel for 3 hours and accurately weighed, to a 25-ml. volumetric flask, add 50 mg. of sodium bisulfite, dissolve in water, dilute to volume with water, and mix. Transfer 2.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with sodium bisulfite solution (1 in 500), and mix. Transfer 5.0 ml. of this solution to a 125-ml. conical flask, add 15.0 ml. of sodium bisulfite solution (1 in 500), and mix.

Assay preparation—Transfer an accurately measured volume of Pyrrocaine Hydrochloride and Epinephrine Injection, equivalent to about 80 mcg. of epinephrine, to a 125-ml. conical flask, add sodium bisulfite solution (1 in 500), if necessary, to make 20.0 ml., and mix.

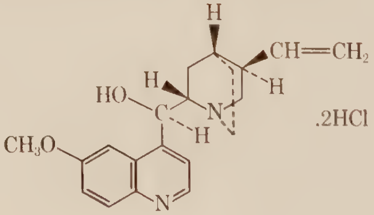
Procedure—Add 10.0 ml. of isopropanol to each of the flasks containing the *Standard preparation* and the *Assay preparation*, mix, and then to each flask add 0.2 ml. of *Ferro-citrate Solution* followed by 2.0 ml. of *Buffer Solution*. Mix, and allow to stand for 5 minutes. Concomitantly determine the absorbances of the solutions, in 5-cm. cells, at the maximum at about 530 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_9H_{13}NO_3$ in each ml. of the Injection taken by the formula $0.02 \times (C/V) \times (0.5497\ A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of epinephrine bitartrate in the *Standard preparation*, V is the volume, in ml., of Injection taken, and 0.5497 is the factor converting epinephrine bitartrate to epinephrine.

Packaging and storage—Preserve Pyrrocaine Hydrochloride and Epinephrine Injection in single-dose containers, preferably of Type I glass.

Injections available—Pyrrocaine Hydrochloride and Epinephrine Injection usually available contains the following amounts of pyrrocaine hydrochloride and epinephrine: 2 percent pyrrocaine hydrochloride with 1:100,000, 1:150,000, or 1:250,000 epinephrine in 1.8-ml. cartridges.

Category and Dose—See Pyrrocaine Hydrochloride.

Quinine Dihydrochloride



$C_{20}H_{24}N_2O_2.2HCl$ Mol. wt. 397.35

Quinine Dihydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{20}H_{24}N_2O_2.2HCl$, calculated on the dried basis.

Description—Quinine Dihydrochloride occurs as a white, odorless powder, having a very bitter taste. It is affected by light. Its solutions are acid.

Solubility—Quinine Dihydrochloride is very soluble in water and is soluble in alcohol. It is slightly soluble in chloroform and very slightly soluble in ether.

Identification—

A: A solution of Quinine Dihydrochloride (1 in 50) is levorotatory.

B: To 5 ml. of a solution of Quinine Dihydrochloride (1 in 1000) add 1 or 2 drops of bromine T.S. and follow with 1 ml. of ammonia T.S.: the liquid acquires an emerald-green color due to the formation of thalleioquin.

C: Quinine Dihydrochloride responds to the tests for *Chloride*, page 808.

Loss on drying, page 814—Dry Quinine Dihydrochloride at 105° for 2 hours: it loses not more than 3 percent of its weight.

Residue on ignition, page 858—Quinine Dihydrochloride yields not more than 0.15 percent of residue on ignition.

Sulfate, page 784—One g. of Quinine Dihydrochloride shows no more sulfate than corresponds to 0.5 ml. of 0.02 *N* sulfuric acid (0.05 percent).

Barium—To 10 ml. of a solution of Quinine Dihydrochloride (1 in 20) add a few drops of diluted sulfuric acid: no turbidity is produced.

Readily carbonizable substances, page 856—Dissolve 200 mg. of Quinine Dihydrochloride in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid M.

Other cinchona alkaloids—Dissolve 1.8 g. of Quinine Dihydrochloride in 10 ml. of water, add a slight excess of ammonia T.S., extract the mixture successively with 20, 10, and 10 ml. of chloroform, and evaporate the combined chloroform solutions to dryness on a steam bath. Dissolve the residue in 25 ml. of alcohol, dilute the solution with 50 ml. of hot water, add 1 *N* sulfuric acid (about 5 ml.) until the solution is acid, using 2 drops of methyl red T.S. as the indicator, and neutralize the excess of acid with 1 *N* sodium hydroxide. Evaporate the solution to dryness on a steam bath, powder the residue, and agitate it in a test tube with 20 ml. of water at 65° for 30 minutes. Cool the mixture to 15°, macerate it at this temperature for 2 hours with occasional shaking, and then filter it through a filter paper (8 to 10 cm.). Transfer 5 ml. of this filtrate, at a temperature of 15°, to a test tube and mix it gently (without shaking) with 6 ml. of ammonia T.S. (which must contain not less than 10 percent and not more than 10.2 percent of NH_3, have a temperature of 15°, and be added at once): a clear liquid is produced.

Assay—

Alcoholic borate electrolyte solution—Mix equal volumes of pH 9.4 alkaline borate buffer solution and dehydrated alcohol.

Sodium bisulfite electrolyte solution—Dissolve 500 mg. of sodium bisulfite in 25 ml. of *Alcoholic borate electrolyte solution*, and filter if necessary to obtain a clear solution. Prepare fresh for each use.

Procedure—Transfer about 100 mg. of Quinine Dihydrochloride, accurately weighed, to a 100-ml. volumetric flask, add 10 ml. of *Sodium bisulfite electrolyte solution*, dilute to volume with *Alcoholic borate electrolyte solution*, and mix. Allow to stand for 10 minutes, then transfer a portion of the solution to a polarographic cell, insert the dropping mercury electrode of a suitable polarograph, and record the polarogram from -1 to -2 volts. Determine the height of the diffusion current $[(i_d)_U]$ as the difference between the residual current and the diffusion current plateau, versus a saturated calomel reference electrode. Concomitantly and similarly determine the diffusion current $[(i_d)_S]$ of a solution containing about 1 mg. per ml. of NF Quinine Dihydrochloride Reference Standard in the same medium as that used for the sample solution. Calculate the quantity, in mg., of $C_{20}H_{24}N_2O_2 . 2HCl$ in the portion of Quinine Dihydrochloride taken by the formula $100C \times [(i_d)_U/(i_d)_S]$, in which C is the exact concentration, in mg. per ml., of the Reference Standard solution.

Packaging and storage—Preserve Quinine Dihydrochloride in well-closed, light-resistant containers.

CATEGORY—Antimalarial.

USUAL DOSE—**1 g.**

Quinine Dihydrochloride Injection

Quinine Dihydrochloride Injection is a sterile solution of quinine dihydrochloride in water for injection. It contains not less than 96.0 percent and not more than 104.0 percent of the labeled amount of $C_{20}H_{24}N_2O_2 . 2HCl$.

Identification—

A: Acidify Quinine Dihydrochloride Injection, previously diluted to a concentration of 1 in 1000, with diluted sulfuric acid: a blue fluorescence is produced.

B: Add 2 or 3 drops of bromine T.S. to 5 ml. of Quinine Dihydrochloride Injection diluted to contain quinine dihydrochloride (1 in 1000) and follow with 1 ml. of ammonia T.S.: the liquid acquires a greenish color due to the formation of thalleioquin.

C: Quinine Dihydrochloride Injection responds to the tests for *Chloride*, page 808.

Other requirements—Quinine Dihydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—Transfer to a separator an accurately measured volume of Quinine Dihydrochloride Injection, equivalent to about 500 mg. of quinine dihydrochloride, and dilute with water, if necessary. Add a slight excess of ammonia T.S., and extract the alkaloid completely with successive portions of chloroform. Evaporate the combined chloroform solutions in a tared beaker, dissolve the residue in 10 ml. of alcohol, evaporate to dryness, dry at 105° for 4 hours, and weigh as $C_{20}H_{24}N_2O_2$. The weight of the anhydrous quinine so obtained, multiplied by 1.225, represents the weight of $C_{20}H_{24}N_2O_2.2HCl$.

Packaging and storage—Preserve Quinine Dihydrochloride Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Quinine Dihydrochloride Injection usually available contains the following amounts of quinine dihydrochloride: 250 mg. in 1 ml.; 300 mg. in 10 ml.; 500 mg. in 1 ml. and in 1.5 ml.; and 1 g. in 2 ml.

CATEGORY and DOSE—See Quinine Dihydrochloride.

Rauwolfia Serpentina

Rauwolfia Serpentina is the dried root of *Rauvolfia serpentina* (Linné) Bentham ex Kurz (Fam. *Apocynaceæ*), sometimes with fragments of rhizome and aerial stem bases attached. It contains not less than 0.15 percent of reserpine-rescinnamine group alkaloids, calculated as reserpine.

Unground Rauwolfia Serpentina Root occurs as segments usually from 5 to 15 cm. in length (pieces sometimes shorter) and from 3 to 20 mm. in diameter. The pieces are subcylindrical to tapering, rather tortuous or curved, rarely branched, but bearing occasional twisted rootlets, which are larger, more abundant, and more rigid and woody on the thicker parts of the roots. Externally, light brown to grayish yellow to grayish brown, dull, rough or slightly wrinkled longitudinally yet peculiarly smooth to the touch, occasionally showing small circular rootlet scars in the larger pieces, with some exfoliation of the bark in small areas to reveal the paler wood beneath. When scraped, the bark separates readily from the wood. Fracture short, but irregular, the longer pieces readily breaking with a snap, slightly fibrous marginally. The freshly fractured surfaces show a rather thin layer of grayish yellow bark, with the pale yellowish white wood constituting about 80 percent of the radius. The smoothed transverse surface of larger pieces shows a finely radiate stele with three or more clearly marked growth rings; a small knob-like protuberance is frequently noticeable at the center. The wood is hard and of relatively low density. The odor is indistinct, earthy, reminiscent of stored white potatoes, and the taste is bitter.

Histology—A transverse section of Rauwolfia Serpentina root shows externally 2 to 8 alternating strata of cork cells, the strata with larger cells alternating with strata made up of markedly smaller cells (*distinction from R. canescens*). Each stratum composed of smaller cells includes from 3 to 5 tangentially arranged cell layers, while each stratum made up of larger cells includes from 1 to 6 tangential layers. In cross-sectional view, the largest central cells of the larger cell group measure 40 to 90 μ radially and up to 75 μ tangentially (although usually smaller), while the cells of the smaller cell groups measure about 5 to 20 μ radially and up to 75 μ tangentially. The walls are thin and suberized. The secondary cortex consists of several rows of tangentially elongated to isodiametric parenchyma cells, most being densely filled with starch grains; others (the short latex cells) occur singly or in short series and contain brown resin masses. The secondary phloem is relatively narrow and is made up of phloem parenchyma (bearing starch grains and less commonly tabular to angular calcium oxalate crystals up to 20 μ long; also, occasionally, with some brown resin masses in outer cells and phloem rays) interlaid with scattered sieve tissue and traversed by phloem rays 2 to 4 cells wide. Sclerenchyma cells (stone cells and fibers) are absent in root (*distinction from other species of Rauwolfia*). Cambium is indistinct, narrow, dark, and wavering. The secondary xylem represents the large bulk of the root and shows one or more prominent annual rings with a denser core of wood about 0.5 mm. across at the center. The xylem is composed of many wood wedges separated by xylem rays, and on closer examination reveals vessels in interrupted radial rows, much xylem parenchyma, many large-celled xylem rays, few wood fibers, and tracheids, all lignified-walled. The xylem fibers occur in both tangential and radial rows. The xylem rays are 1 to 12, occasionally up to 16, cells in width.

Rauwolfia Serpentina Rhizome—Histology—Similar to that of root except for the presence of a prominent cortex, pericycle fibers, bicollateral vascular bundles, and a small central pith. The pericycle fibers occur singly or in groups of 2 to 5, have thick, nonlignified walls, tapering, often lobed ends, with subterminal enlargements having thin walls and broad lumina. Vessel elements up to 485 μ are found. The xylem rays are 1 to 4 cells wide, with lignified and pitted walls. Internal phloem strands occur embedded in the outer region of the pith. The xylem fibers are somewhat less wavy than those of the root. The pith consists of starch parenchyma cells, among which are scattered short latex cells with yellowish contents stained brown with iodine T.S.

Ground Rauwolfia Serpentina Root—Brownish to reddish gray in color. Present are very numerous starch grains (mostly simple, 2- to 3-compound occasionally 4-compound); simple grains spheroid, ovate, muller-shaped, plano- to angular-convex, or irregular; hilum simple, Y-shaped, stellate, or irregularly cleft; unaltered grains 6 to 34 μ (average 20 μ) in diameter, mostly in the lower range (maximum sizes larger than in *R. canescens* and *R. micrantha*); altered grains up to about 50 μ in diameter; large unaltered grains show polarization cross clearly; calcium oxalate prisms and cluster crystals scattered, about 10 to 15 μ in size; brown resin masses and yellowish granular secretion masses occur occasionally; isolated cork cells elongated, up to 90 μ in length; phelloderm and phloem parenchyma cells similar in appearance; vessels subcylindrical, up to 360 μ long and from about 20 up to 57 μ in diameter (narrower than in *R. canescens*) (the wall markings generally consist of simple pits, with bordered pits adjacent to xylem ray cells), the vessel end walls oblique to transverse, generally with openings in the end walls, some vessels showing tyloses; tracheids pitted, with moderately thick, tapering, beaded walls, with relatively broad lumina, polygonal in cross-section; xylem parenchyma cells with moderately thick walls with simple circular pits, cells polygonal in cross-section, bearing considerable starch; phloem and xylem-ray cells with pitted walls bearing much starch, sometimes with brown resin masses, xylem fibers with thick heavily lignified walls showing small transverse and oblique linear pits and pointed simple to bifurcate ends, measuring from 200 to 750 μ long (shorter than in *R. micrantha* and *R. canescens*). No phloem fibers or sclereids are present in root (colorless nonlignified pericycle or primary phloem fibers, single or in small groups, may be present from rhizome or stem tissues).

Acid-insoluble ash, page 885—Rauwolfia Serpentina yields not more than 2 percent of acid-insoluble ash.

Stems and other foreign organic matter, page 885—Rauwolfia Serpentina contains not more than 2 percent of stem and not more than 3 percent of other foreign organic matter.

Chemical identification—

Formamide—Distil under vacuum using all-glass apparatus (b.p. 101° at 12 mm. Hg). Store in a desiccator over sulfuric acid.

Immobile solvent—Dilute 30 ml. of formamide to 100 ml. with acetone.

Mobile solvent A—Mix 90 ml. of isooctane, 60 ml. of carbon tetrachloride, 4 ml. of piperidine, and 2 ml. of *tert*-butyl alcohol.

Mobile solvent B—Mix 75 ml. of chloroform, 75 ml. of isooctane, and 2 ml. of *tert*-butyl alcohol.

Spray solution—Dissolve 25 g. of trichloroacetic acid in 100 ml. of methanol.

Standard solution—Warm a 1-g. portion of NF Rauwolfia Serpentina Reference Standard with 5 ml. of alcohol at 55° to 65° for 30 minutes with occasional mixing. Cool, and filter.

Sample preparation—Reduce 10 g. of Rauwolfia Serpentina root to a fine powder. Treat a 1-g. portion as in the preparation of the *Standard solution*.

Procedure A—Line the sides of a chromatographic chamber, suitable for ascending chromatography (see *Chromatography*, page 786), with blotting paper. Transfer *Mobile solvent A* to the bottom of the container. Cover the chamber. Immerse a 20 × 20-cm. sheet of filter paper (Whatman No. 1 or its equivalent) in the *Immobile solvent* and blot between paper toweling. Allow the acetone solvent to evaporate completely. On a line one inch from the bottom of the filter paper, spot with about 1-μl. portions of the *Sample preparation* and of the *Standard solution*. Allow to dry. Apply a 2-μl. portion of the *Immobile solvent* to each spot, allow to dry and suspend the paper so that it dips into the *Mobile solvent*. Cover the chamber and after about one hour, when the *Mobile solvent* has risen approximately $^7/_8$ of the height of the paper, remove the chromatogram and dry at 90° in a current of air. Spray the paper lightly and evenly with the *Spray solution* and re-dry at 90° for 10 minutes.

Procedure B—Use the apparatus described in *Procedure A*, but containing a glass trough with about 2 ml. of stronger ammonia T.S. to saturate the atmosphere of the tank with NH_3. Transfer *Mobile solvent B* to the bottom of the tank outside of the trough. Complete the test as described in *Procedure A*, omitting the trichloroacetic acid spray.

Examine both chromatograms under ultraviolet light and note the fluorescent spots. In *both chromatograms* the *Sample preparation* yields spots corresponding in position and color to those of the *Standard solution*.

Loss on drying, page 814—Dry Rauwolfia Serpentina to constant weight at 100°: it loses not more than 12 percent of its weight.

Salmonella, page 862—The test for *Salmonella* in Rauwolfia Serpentina (as the ground root) is negative.

Assay—*Apparatus*—A medium-sized continuous extraction apparatus provided with a 250-ml. flask and a 35 × 80-mm. thimble is most convenient, although a smaller apparatus may be used.

Solvents—Alcohol, chloroform, and 1,1,1-trichloroethane—Redistil the trichloroethane in an all-glass apparatus, and collect the fraction boiling between 73° and 76°.

Standard solution—Dissolve 20.0 mg. of USP Reserpine Reference Standard in 25 ml. of hot alcohol, cool, and dilute to 50.0 ml. with alcohol. When stored in a tightly-stoppered, light-resistant bottle in the dark, this solution is chromogenically stable for several weeks. Dilute 5.0 ml. to 100.0 ml. with alcohol, before using.

Procedure—Extract about 2.5 g. of finely powdered Rauwolfia Serpentina, accurately weighed, in a continuous extraction apparatus for 4 hours. Use about 100 ml. of vigorously boiling alcohol as solvent, and a few boiling chips to prevent bumping. Protect the flask and thimble, and all solutions of Rauwolfia Serpentina alkaloids from direct or strong light.

Wash the extract into a 100-ml. volumetric flask with alcohol, cool, dilute to volume, and mix. Pipet 20.0 ml. into a separator containing 200 ml. of approximately 0.5 N sulfuric acid, mix, and extract with three successive 25-ml. portions of trichloroethane. Lubricate stopcocks only with lubricants insoluble in trichloroethane or chloroform (saliva is satisfactory). Drain the lower phase as completely as possible. Wash each of the trichloroethane extracts in a second separator containing 50 ml. of the 0.5 N sulfuric acid, and discard the trichloroethane extracts.

Extract the weakly basic alkaloids from the first acid solution with 25-, 15-, 15-, 10-, 10-, and 10-ml. portions of chloroform. Wash each chloroform extract with the acid in the second separator, then with two 10-ml. portions of sodium bicarbonate solution (1 in 50) in two additional separators. Filter the chloroform extracts through chloroform-washed cotton into a 100-ml. volumetric flask containing 10 ml. of alcohol. Dilute to volume with alcohol, and mix.

Transfer duplicate 10.0-ml. aliquots to 150 × 18-mm. test tubes and mix with 4 ml. of alcohol. Add a few boiling chips, and heat to boiling in a water bath below 70°. Raise the bath temperature, and heat continuously to evaporate the solution *almost* to dryness. Wipe the outsides of the warm tubes, place in a vacuum desiccator, and evaporate to dryness. Dissolve the residues by agitating with 5.0 ml. of alcohol. Transfer duplicate 5.0-ml. aliquots of the *Standard solution* to test tubes. Add 2.0 ml. of 0.5 N sulfuric acid to one of the sample tubes and to one of the standard tubes (the blanks). Add to the other tubes 1.0 ml. of 0.5 N sulfuric acid, and 1.0 ml. of 0.3 percent sodium nitrite solution. Mix the contents of each tube, and warm in a water bath at 50° to 60° for 20 minutes. Cool, add to each tube 0.5 ml. of sulfamic acid solution (1 in 20), and mix. After stabilization of the solutions, determine their absorbances in 1-cm. cells at 390 mμ relative to a mixture of 2 parts alcohol and 1 part water. The quantity of reserpine-rescinnamine group alkaloids, in mg., in the sample weighed is given by the formula: $5(A - A_0)/(S - S_0)$, where A and A_0 are the absorbances of the nitrite-treated sample and sample blank, respectively, and S and S_0 are the corresponding absorbances for the solutions from the respective *Standard solution* aliquots.

Packaging and storage—Preserve Rauwolfia Serpentina in well-closed containers in a cool, dry place, secure against insect attack (see page 14).

CATEGORY—Antihypertensive.

USUAL DOSE—Initial, **200 mg.** daily for 1 to 3 weeks; maintenance, **50** to **300 mg.** daily.

Powdered Rauwolfia Serpentina

Powdered Rauwolfia Serpentina is rauwolfia serpentina reduced to a fine or a very fine powder, and adjusted if necessary to conform to the official requirements for reserpine-rescinnamine group alkaloids by admixture with lactose or starch or with a powdered rauwolfia serpentina containing a higher or lower content of these alkaloids. It contains not less than 0.15 percent and not more than 0.20 percent of reserpine-rescinnamine group alkaloids, calculated as reserpine.

Description and identification—Powdered Rauwolfia Serpentina conforms to the description for *Ground Rauwolfia Serpentina Root* and to the *Chemical identification test* under *Rauwolfia Serpentina*, page 618.

Acid-insoluble ash, page 885—Powdered Rauwolfia Serpentina yields not more than 2 percent of acid-insoluble ash.

Salmonella, page 862—The test for *Salmonella* in Powdered Rauwolfia Serpentina is negative.

Assay—Proceed as directed in the *Assay* under *Rauwolfia Serpentina*, page 618.

Packaging and storage—Preserve Powdered Rauwolfia Serpentina in well-closed containers in a cool, dry place, secure against insect attack (see page 14).

CATEGORY and DOSE—See Rauwolfia Serpentina.

Rauwolfia Serpentina Tablets

Rauwolfia Serpentina Tablets contain an amount of reserpine-rescinnamine group alkaloids, calculated as reserpine, equivalent to not less than 0.15 percent and not more than 0.20 percent of the labeled amount of powdered rauwolfia serpentina.

Identification—The powdered rauwolfia serpentina in the Tablets conforms to the description of *Ground Rauwolfia Serpentina Root* and to the *Chemical identification test* under *Rauwolfia Serpentina,* page 618.

Disintegration, page 878—The disintegration time limit for Rauwolfia Serpentina Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Rauwolfia Serpentina Tablets meet the requirements of the content uniformity test for tablets.

Salmonella, page 862—The test for *Salmonella* in Rauwolfia Serpentina Tablets is negative.

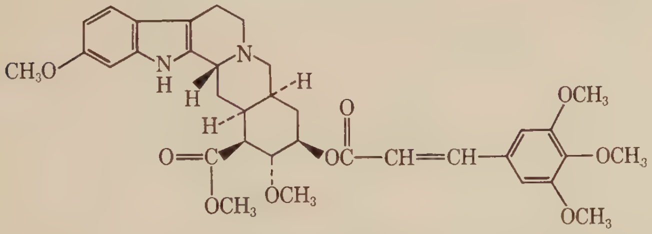
Assay—Weigh and finely powder not less than 20 Rauwolfia Serpentina Tablets. Weigh accurately a portion of this powder, equivalent to 2.5 g. of powdered rauwolfia serpentina, and proceed as directed for *Procedure* in the *Assay* under *Rauwolfia Serpentina,* page 618, beginning with "Extract . . . in a continuous extraction apparatus . . . ."

Packaging and storage—Preserve Rauwolfia Serpentina Tablets in tight, light-resistant containers.

Tablets available—Rauwolfia Serpentina Tablets usually available contain the following amounts of powdered rauwolfia serpentina: **50** and **100 mg.**

Category and Dose—See Rauwolfia Serpentina.

Rescinnamine



Methyl 18β-Hydroxy-11,17α-dimethoxy-3β,20α-yohimban-16β-carboxylate 3,4,5-Trimethoxycinnamate (Ester)

$C_{35}H_{42}N_2O_9$ Mol. wt. 634.73

Rescinnamine, dried at 60° for 3 hours, contains not less than 95.0 percent and not more than 101.0 percent of $C_{35}H_{42}N_2O_9$.

Description—Rescinnamine occurs as a white or pale buff to cream colored, odorless, crystalline powder. It darkens slowly on exposure to light, but more rapidly when in solution.

Solubility—Rescinnamine is soluble in chloroform and in acetic acid. It is slightly soluble in alcohol, and practically insoluble in water.

Identification—To about 2 ml. of glacial acetic acid add 4 drops of *Solution 2* obtained in the *Assay preparation* under *Assay,* mix, and add 4 ml. of a solution of vanillin in hydrochloric acid (1 in 50): a pink color develops within a few minutes or as a result of warming the solution for 10 to 20 seconds.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Rescinnamine, previously dried at 60° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Rescinnamine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—Transfer 5.0 ml. of *Solution 1* obtained in the *Standard preparation* under *Assay* to a 50-ml. volumetric flask, dilute to volume with chloroform, and mix. Also transfer 5.0 ml. of *Solution 2* obtained in the *Assay preparation* under *Assay* to a second 50-ml. volumetric flask, dilute to volume with chloroform, and mix. Dilute 10.0-ml. portions of each solution to 25.0 ml. with alcohol, and mix. Determine the absorbances of the solutions in the range of 230 mμ to 350 mμ, with a suitable spectrophotometer, using a mixture of chloroform and alcohol (9:16) as the blank. The absorption spectrum of the solution of Rescinnamine exhibits maxima and minima at the same wavelengths as that of the solution of NF Rescinnamine Reference Standard, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance, occurring at about 305 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Rescinnamine, previously dried at 60° for 3 hours, determined in a solution in chloroform containing 100 mg. of Rescinnamine in each 10 ml., is between −87° and −97°.

Loss on drying, page 814—Dry Rescinnamine at 60° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Rescinnamine yields not more than 0.1 percent of residue on ignition.

Assay—NOTE: Perform the dilution and extraction operations and the *Procedure* quickly, without exposure to direct sunlight.

Standard preparation—Transfer 20.0 mg. of NF Rescinnamine Reference Standard, previously dried at 60° for 3 hours, to a 50-ml. volumetric flask, dissolve in 0.5 ml. of chloroform, dilute to volume with alcohol, and mix (*Solution 1*). Protect the solution from light. Just prior to use in the *Assay*, transfer 5.0 ml. of the solution to a second 50-ml. volumetric flask, dilute to volume with chloroform, and mix.

Assay preparation—Transfer 20 mg. of Rescinnamine, previously dried at 60° for 3 hours and accurately weighed, to a 50-ml. volumetric flask, dissolve in 0.5 ml. of chloroform, dilute to volume with alcohol, and mix (*Solution 2*). Protect the solution from light. Pipet 5.0 ml. of the solution into a 125-ml. separator, add 50 ml. of 0.5 *N* sulfuric acid, and extract with 20 ml. of chloroform, shaking thoroughly for 2 minutes. Transfer the chloroform layer to a second 125-ml. separator, retaining the acid solution, add 50 ml. of sodium bicarbonate solution (1 in 100) to the second separator, and shake thoroughly for 2 minutes. Filter the chloroform phase through chloroform-washed cotton into a 50-ml. volumetric flask containing 5.0 ml. of alcohol. Extract the sulfuric acid and sodium bicarbonate wash solutions with two 10-ml. portions of chloroform, filtering the two extracts into the volumetric flask, dilute to volume with chloroform, and mix.

Procedure—Transfer duplicate 10.0-ml. aliquots of the *Standard preparation* and duplicate 10.0-ml. aliquots of the *Assay preparation* to separate 25-ml. volumetric flasks. To each flask add 10.0 ml. of dilute hydrochloric acid in alcohol (5 in 100). To one of the flasks from the *Standard preparation* and to one from the *Assay preparation* add 1.0 ml. of a solution of sodium nitrite in alcohol (1 in 500), followed by 10 drops of hydrochloric acid. To the remaining flasks, which constitute the blanks for the respective preparations, add 1.0 ml. of alcohol and 10 drops of hydrochloric acid. Mix the contents of each flask, and allow to stand for 30 minutes. Add 1.0 ml. of a solution of ammonium sulfamate (1 in 40) to each flask, dilute to volume with alcohol, mix, and allow to stand for 10 minutes. Determine the absorbance of each solution in 1-cm. cells, at the maximum at about 390 mμ, with a suitable spectrophotometer, relative to the absorbance of a mixture of chloroform, alcohol, and water (9:15:1). Record the absorbance of the solution from the *Standard preparation* as S, that from the *Assay preparation* as A, that of the blank from the *Standard preparation* as S_0, and that of the blank from the *Assay preparation* as A_0. Calculate the quantity, in mg., of $C_{35}H_{42}N_2O_9$ in the Rescinnamine taken by the formula $20 \times (A - A_0)/(S - S_0)$.

Packaging and storage—Preserve Rescinnamine in tight, light-resistant containers.

CATEGORY—Antihypertensive.

USUAL DOSE—Initial, **500 mcg.** one or two times a day for up to 2 weeks. Maintenance, **250 mcg.** daily.

USUAL DOSE RANGE—**250 mcg.** to **2 mg.** daily.

Rescinnamine Tablets

Rescinnamine Tablets contain not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{35}H_{42}N_2O_9$.

Identification—Transfer to a test tube about 3 ml. of the final chloroform solution obtained from Rescinnamine Tablets as directed under *Assay preparation* in the *Assay* and evaporate almost to dryness. To the residue add 0.5 ml. of glacial acetic acid, swirl for 1 to 2 minutes, and add 1 ml. of a solution of vanillin in hydrochloric acid (1 in 50): a pink color is produced within a few minutes, or as a result of warming the solution for 10 to 20 seconds.

Disintegration, page 878—The disintegration time limit for Rescinnamine Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Rescinnamine Tablets meet the requirements of the content uniformity test for tablets.

Other alkaloids—Transfer 10.0 ml. each of the *Assay preparation* and the *Standard preparation* obtained in the *Assay* to separate 25-ml. volumetric flasks, dilute each to volume with alcohol, and mix. Determine the absorption spectrum by the procedure used in the *Ultraviolet absorption test* under *Rescinnamine,* page 621. The spectrum is similar to that of the NF Rescinnamine Reference Standard. Calculate the quantity, in mg., of $C_{35}H_{42}N_2O_9$ in the portion of the Tablets taken by the formula $2.5 \times (T/S)$, in which T and S are the absorbances of the solutions representing the Tablets and the NF Rescinnamine Reference Standard, respectively, at the absorption maximum near 305 mμ. The result thus obtained does not differ from the result obtained in the *Assay* by more than 8 percent.

Assay—NOTE: Perform the dilution and extraction operations and the *Procedure* quickly, without exposure to direct sunlight.

Standard preparation—Prepare as directed in the *Assay* under *Rescinnamine,* page 621.

Assay preparation—Weigh and finely powder not less than 20 Rescinnamine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 2.5 mg. of rescinnamine, to a 50-ml. beaker, add 10 ml. of alcohol, and boil gently on a steam bath for 20 minutes, maintaining a constant volume by the occasional addition of small portions of alcohol. Cool, add 5 ml. of chloroform, mix, and filter through chloroform-washed cotton into a 25-ml. volumetric flask. Wash the beaker and filter with additional small portions of chloroform, dilute to volume with chloroform, and mix. Pipet 20.0 ml. of the solution into a 125-ml. separator, and add 10 ml. of chloroform and 50 ml. of 0.5 *N* sulfuric acid. Shake thoroughly for 2 minutes, and proceed as directed for *Assay preparation* in the *Assay* under *Rescinnamine,* page 621, beginning with "Transfer the chloroform layer . . . ."

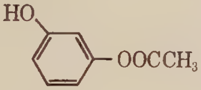
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Rescinnamine,* page 621. Calculate the quantity, in mg., of $C_{35}H_{42}N_2O_9$ in the portion of the Tablets taken by the formula $2.5 \times (A - A_0)/(S - S_0)$, where the symbols are defined as in the *Assay* under *Rescinnamine,* page 621.

Packaging and storage—Preserve Rescinnamine Tablets in tight, light-resistant containers.

Tablets available—Rescinnamine Tablets usually available contain the following amounts of rescinnamine: 250 and 500 mcg.

CATEGORY and DOSE—See Rescinnamine.

Resorcinol Monoacetate



$C_8H_8O_3$ Mol. wt. 152.15

Description—Resorcinol Monoacetate is a viscous, pale yellow or amber liquid with a faint characteristic odor and a burning taste. It boils at about 283° with decomposition. A saturated solution of Resorcinol Monoacetate is acid to litmus.

Solubility—Resorcinol Monoacetate dissolves in alcohol and in most organic solvents. It is sparingly soluble in water.

Identification—

A: Fuse 3 drops of Resorcinol Monoacetate with about 300 mg. of phthalic anhydride and about 50 mg. of zinc chloride: a small portion of the fused mixture when dissolved in 10 ml. of sodium hydroxide T.S. produces an intense blue fluorescence typical of fluorescein.

B: Dissolve 0.5 ml. of Resorcinol Monoacetate in 3 ml. of alcohol, add 3 drops of sulfuric acid and boil: ethyl acetate, recognizable by its odor, is evolved.

Specific gravity, page 866—The specific gravity of Resorcinol Monoacetate is not less than 1.203 and not more than 1.207.

Acidity—A solution of 10 ml. of Resorcinol Monoacetate in 20 ml. of benzene, when shaken with 100 ml. of water, requires not more than 0.5 ml. of 0.1 *N* sodium hydroxide for neutralization, using methyl orange T.S. as the indicator.

Loss on drying, page 814—Dry Resorcinol Monoacetate on a steam bath for 1 hour: it loses not more than 2.5 percent of its weight.

Residue on ignition, page 858—Resorcinol Monoacetate yields not more than 0.1 percent of residue on ignition.

Packaging and storage—Preserve Resorcinol Monoacetate in tight, light-resistant containers.

CATEGORY—Antiseborrheic; keratolytic.

FOR EXTERNAL USE—In topical preparations for application to the scalp.

Compound Resorcinol Ointment

Resorcinol	60 g.
Zinc Oxide	60 g.
Bismuth Subnitrate	60 g.
Juniper Tar	20 g.
Yellow Wax	100 g.
Petrolatum	290 g.
Anhydrous Lanolin	280 g.
Glycerin	130 g.
To make	1000 g.

Melt the yellow wax and anhydrous lanolin in a dish on a steam bath. Triturate the zinc oxide and bismuth subnitrate with the petrolatum until smooth, and add it to the melted mixture. Dissolve the resorcinol in the glycerin; incorporate the solution with the warm mixture just prepared; then add the juniper tar, and stir the Ointment until it congeals.

Packaging and storage—Preserve Compound Resorcinol Ointment in tight containers and avoid prolonged exposure to temperatures above 30°.

CATEGORY—Local antifungal; keratolytic.

FOR EXTERNAL USE—Topically to the skin as required.

Ringer's Solution

Ringer's Solution is a solution of NaCl (sodium chloride), KCl (potassium chloride), and $CaCl_2 . 2H_2O$ (calcium chloride) in purified water. It contains, in each 100 ml., not less than 323.0 mg. and not more than 354.0 mg. of sodium (Na, equivalent to not less than 820.0 mg. and not more than 900.0 mg. of NaCl); not less than 13.0 mg. and not more than 18.0 mg. of potassium (K, equivalent to not less than 25.0 mg. and not more than 35.0 mg. of KCl); not less than 8.20 mg. and not more than 9.80 mg. of calcium (Ca, equivalent to not less than 30.0 mg. and not more than 36.0 mg. of $CaCl_2 . 2H_2O$); and not less than 523.0 mg. and not more than 580.0 mg. of chloride (Cl, as NaCl, KCl, and $CaCl_2 . 2H_2O$).

Caution: Do not use Ringer's Solution for parenteral administration or in preparations to be used parenterally. For such purposes use Ringer's Injection, USP XVIII.

Sodium Chloride	8.6 g.
Potassium Chloride	0.30 g.
Calcium Chloride	0.33 g.
Purified Water, recently boiled, a sufficient quantity,	
To make	1000 ml.

Dissolve the three salts in a sufficient quantity of recently boiled purified water to make 1000 ml., and filter until clear.

pH, page 824—The pH of Ringer's Solution is between 5.0 and 7.5.

Arsenic—A *Test Preparation* prepared by evaporation of 100.0 ml. of Ringer's Solution to 35 ml. meets the requirements of the *Arsenic Test,* page 777 (0.1 part per million As).

Heavy metals, page 806—To 20 ml. of Ringer's Solution add 2 ml. of diluted acetic acid and sufficient water to make 25 ml.: the heavy metals limit for Ringer's Solution is 0.3 part per million.

Assay for calcium—Pipet 50.0 ml. of Ringer's Solution into a 250-ml. beaker, add 15 ml. of sodium hydroxide T.S., and 300 mg. of hydroxy naphthol blue and titrate with 0.005 *M* disodium ethylenediaminetetraacetate until the solution is deep blue in color. Each ml. of 0.005 *M* disodium ethylenediaminetetraacetate is equivalent to 200.4 mcg. of Ca.

Assay for potassium—

Standard solutions—Prepare five standard solutions (*1*, *2*, *3*, *4*, and *5*) each containing about 0.02 percent of a suitable nonionic wetting agent and 1.093 g. of sodium chloride per 1000 ml., and to the solutions add, respectively 0-, 5-, 10-, 15-, and 20-mg. supplements of potassium, in the form of the chloride, per 1000 ml., and mix. If necessary, because of changes in the sensitivity of the instrument mentioned below, vary the levels of concentration of the potassium, keeping the ratios between solutions approximately as given.

Standard graph—Set a suitable flame photometer for maximum transmittance at a wavelength of 766 mμ to 767 mμ. (The exact wavelength setting will vary slightly with the instrument.) Adjust the instrument to zero transmittance with solution *1*. Then adjust the instrument to 100 percent transmittance with solution *5*. Read the percentage transmittance of solutions *2*, *3*, and *4*. Plot the observed transmittance of solutions *2*, *3*, *4*, and *5* as the ordinate and the concentration of potassium as the abscissa on arithmetic coordinate paper.

Procedure—Pipet a volume of Ringer's Solution, equivalent to about 17 mg. of potassium or a quantity corresponding to the concentration of the *Standard solutions*, into a 1000-ml. volumetric flask. Add 0.02 percent of a suitable nonionic wetting agent, dilute to volume with water, and mix. Adjust the instrument to zero transmittance with solution *1*, and to 100 percent transmittance with solution *5*. Read the percentage transmittance of the test solution, and, by reference to the standard potassium graph, calculate the potassium content of the sample in mg. of potassium per 100 ml.

Assay for sodium—Proceed as directed under *Assay for potassium*, with the following modifications: (1) prepare the *Standard solutions* to contain 0, 5, 10, 15, and 20 mg. of sodium, in the form of the chloride, per 1000 ml., without added potassium; (2) prepare the *Standard graph* with the flame photometer set for maximum transmittance at a wavelength of 588 mμ to 589 mμ; and (3) under *Procedure* read "sodium" for "potassium" throughout.

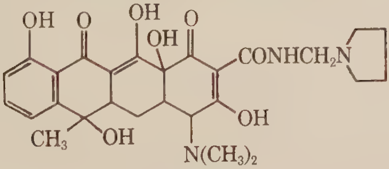
Assay for chloride—Pipet 20.0 ml. of Ringer's Solution into a glass-stoppered flask, and add 25 ml. of water. Add 3 ml. of nitric acid, previously diluted with 5 ml. of water, then, while agitating the mixture, slowly add 50.0 ml. of 0.1 *N* silver nitrate. Add 5 ml. of nitrobenzene, shake vigorously for 1 minute, add 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 3.545 mg. of Cl.

Packaging and storage—Preserve Ringer's Solution in tight containers.

Category—Irrigation solution (physiological salt solution).

For external use—Topically as required.

Rolitetracycline*



4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-*N*-(1-pyrrolidinylmethyl)-2-naphthacenecarboxamide

$C_{27}H_{33}N_3O_8$ Mol. wt. 527.58

Rolitetracycline has a potency of not less than 900.0 mcg. per mg., calculated on the anhydrous basis. Rolitetracycline conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Rolitetracycline occurs as a light yellow, crystalline powder having a characteristic, musty, amine-like odor.

Solubility—Rolitetracycline is soluble in water and acetone, and is slightly soluble in absolute ethyl alcohol. It is very slightly soluble in ether.

Packaging and storage—Preserve Rolitetracycline in tight containers.

Category—Antibacterial.

Usual dose range—Intramuscular, **150 mg.** to **350 mg.** every 12 hours; intravenous infusion, **350 mg.** to **700 mg.** every 12 hours.

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* Patented. See notice, page ii.

Rolitetracycline for Injection

Rolitetracycline for Injection is a sterile, dry mixture of Rolitetracycline and one or more suitable buffer substances. It contains not less than 90.0 percent of the labeled amount of $C_{27}H_{33}N_3O_8$. Rolitetracycline for Injection conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Rolitetracycline for Injection in *Containers for Sterile Solids* as described under *Injections,* page 810.

Sizes available—Rolitetracycline for Injection usually available contains the following amounts of rolitetracycline: 150, 350, and 700 mg.

CATEGORY and DOSE—See Rolitetracycline.

Rose Oil

Rose Oil is the volatile oil distilled with steam from the fresh flowers of *Rosa gallica* Linné, *Rosa damascena* Miller, *Rosa alba* Linné, *Rosa centifolia* Linné, and varieties of these species (Fam. *Rosaceæ*).

Description—Rose Oil is a colorless or yellow liquid, having the characteristic odor and taste of rose. At 25° it is a viscous liquid. Upon gradual cooling it changes to a translucent, crystalline mass, which may be liquefied easily by warming.

Solubility test—One ml. of Rose Oil is miscible with 1 ml. of chloroform without turbidity. Add 20 ml. of 90 percent alcohol to this mixture: the resulting liquid is neutral or acid to moistened litmus paper and, upon standing at 20°, deposits crystals within 5 minutes.

Specific gravity, page 866—The specific gravity of Rose Oil is between 0.848 and 0.863 at 30° compared with water at 15°.

Angular rotation, page 822—The angular rotation of Rose Oil, determined in a 100-mm. tube, is not less than $-1°$ and not more than $-4°$.

Refractive index, page 858—The refractive index of Rose Oil at 30° is not less than 1.457 and not more than 1.463.

Packaging and storage—Preserve Rose Oil in well-filled, tight containers.

CATEGORY—Perfume.

Stronger Rose Water

Stronger Rose Water is a saturated solution of the odoriferous principles of the flowers of *Rosa centifolia* Linné (Fam. *Rosaceæ*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

NOTE: Stronger Rose Water, diluted with an equal volume of purified water, may be supplied when "Rose Water" is required.

Description—Stronger Rose Water is nearly colorless and clear, possessing the pleasant odor and taste of fresh rose blossoms. It must be free from empyreuma, mustiness, and fungal growths.

Reaction—Stronger Rose Water is neutral or acid to litmus.

Residue on evaporation—Evaporate 100 ml. of Stronger Rose Water on a steam bath, and dry the residue at 105° for 1 hour: not more than 15 mg. of residue remains (0.015 percent).

Heavy metals, page 806—Add 2 ml. of diluted acetic acid to 5 ml. of Stronger Rose Water and add sufficient water to make 25 ml.: the heavy metals limit for Stronger Rose Water is 2 parts per million.

Packaging and storage—The odor of Stronger Rose Water is best preserved by allowing a limited access of fresh air to the container.

CATEGORY—Perfume.

Rose Water Ointment

Spermaceti	**125**	**g.**
White Wax	**120**	**g.**
Almond Oil	**560**	**g.**
Sodium Borate	**5**	**g.**
Stronger Rose Water	**25**	**ml.**
Purified Water	**165**	**ml.**
Rose Oil	**0.2**	**ml.**
To make about	**1000**	**g.**

Reduce the spermaceti and the white wax to small pieces, melt them on a steam bath, add the almond oil, and continue heating until the temperature of the mixture reaches 70°. Dissolve the sodium borate in the purified water and stronger rose water, warmed to 70°, and gradually add the warm solution to the melted mixture, stirring rapidly and continuously until it has cooled to about 45°. Then incorporate the rose oil.

Rose Water Ointment must be free from rancidity. If the Ointment has been chilled, warm it slightly before attempting to incorporate other ingredients (see page 8).

Packaging and storage—Preserve Rose Water Ointment in tight, light-resistant containers.

CATEGORY—Emollient; ointment base.
FOR EXTERNAL USE—Topically to skin.

Rosin

Rosin is the solid resin obtained from *Pinus palustris* Miller, and from other species of *Pinus* Linné (Fam. *Pinaceæ*).

Description—Rosin occurs as sharply angular, translucent, amber-colored fragments, frequently covered with a yellow dust. The fracture is brittle at ordinary temperatures, shiny, and shallow-conchoidal. The odor and taste are slightly terebinthinate. Rosin is easily fusible and burns with a dense, yellowish smoke.

Solubility—Rosin dissolves in alcohol, in ether, in benzene, in glacial acetic acid, and in fixed and volatile oils. It is also soluble in dilute solutions of the fixed alkali hydroxides.

Specific gravity, page 866—The specific gravity of Rosin is not less than 1.07 and not more than 1.09.

Residue on ignition, page 858—Rosin yields not more than 0.1 percent of residue on ignition.

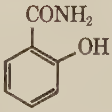
Acid value, page 804—The acid value of Rosin is not less than 150, using about 1 g. of Rosin, accurately weighed.

Packaging and storage—Preserve Rosin in well-closed containers.

CATEGORY—Stiffening agent.

Rubbing Alcohol, page 26
Rubbing Alcohol, Isopropyl, page 383
Saccharin, Calcium, page 129
Saccharin, Calcium, and Calcium Cyclamate Solution, page 120
Saccharin, Calcium, and Calcium Cyclamate Tablets, page 121
Saccharin, Sodium, page 657
Saccharin, Sodium, Tablets, page 658
Saccharin, Sodium, and Sodium Cyclamate Solution, page 644
Saccharin, Sodium, and Sodium Cyclamate Tablets, page 644

Salicylamide



$C_7H_7NO_2$ Mol. wt. 137.14

Salicylamide contains not less than 98.0 percent and not more than 102.0 percent of $C_7H_7NO_2$, calculated on the anhydrous basis.

Description—Salicylamide occurs as a white, almost odorless, crystalline powder.

Solubility—Salicylamide is slightly soluble in water. It is soluble in alcohol and in propylene glycol, and is sparingly soluble in ether and in chloroform. It is freely soluble in solutions of alkalies.

Identification—

A: Dissolve about 100 mg. of Salicylamide in 5 ml. of alcohol and add a few drops of ferric chloride T.S.: a violet color develops.

B: Dissolve about 200 mg. of Salicylamide in 5 ml. of alcohol, dilute the solution to 20 ml. with water and add bromine T.S. slowly with shaking, until a yellow color persists. Allow the mixture to stand at room temperature for about 30 minutes, collect the precipitate on a filter, wash it with water, and recrystallize it from diluted alcohol. Filter and dry the crystals so obtained in a vacuum desiccator over phosphorus pentoxide: the 3,5-dibromosalicylamide melts between 183° and 185°, page 814.

Melting range, page 814—Salicylamide melts between 139° and 142°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Salicylamide, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Salicylamide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 62,500 solution of Salicylamide in methanol exhibits maxima and minima at the same wavelengths as that of NF Salicylamide Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance occurring at about 302 mμ, do not differ by more than 3 percent.

Water, page 900—Determine the water content of Salicylamide by the titrimetric method: not more than 0.5 percent is found.

Residue on ignition, page 858—Salicylamide yields not more than 0.05 percent of residue on ignition.

Assay—Transfer about 500 mg. of Salicylamide, accurately weighed, to a 100-ml. beaker equipped with a mechanical stirrer and a suitable cover with a single hole for the buret tip. Add 30 ml. of freshly neutralized dimethylformamide containing a few drops of thymol blue T.S. Titrate with 0.1 *N* sodium methoxide to the same blue end-point obtained in the standardization of the sodium methoxide solution. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium methoxide is equivalent to 13.71 mg. of $C_7H_7NO_2$.

Packaging and storage—Preserve Salicylamide in well-closed containers.

CATEGORY—Analgesic.

USUAL DOSE—**300** to **600 mg.** every 3 or 4 hours. Child's dose—**75 mg.** for each year of age repeated every 3 or 4 hours with a maximum single dose of **300 mg.**

Salicylamide Oral Suspension

Salicylamide Oral Suspension contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_7H_7NO_2$.

Identification—Evaporate to dryness a suitable volume of the *Assay preparation*, prepared as directed in the *Assay:* the infrared absorption spectrum of a potassium bromide dispersion prepared from the residue exhibits maxima at the same wavelengths as that of NF Salicylamide Reference Standard, similarly measured.

pH, page 824—The pH of Salicylamide Oral Suspension is between 5.0 and 7.0.

Assay—Transfer an accurately measured volume of Salicylamide Oral Suspension, equivalent to about 200 mg. of salicylamide, to a 60-ml. separator, add 20 ml. of water and 1.5 ml. of diluted hydrochloric acid, and extract with three 25-ml. portions of ether. Filter each extract through anhydrous sodium sulfate, and evaporate the filtrate to dryness on a steam bath. Dissolve the residue in sufficient methanol to make 100.0 ml. Transfer 20.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 10.0 ml. of this last solution to a 100.0 ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Salicylamide Reference Standard, in the same medium at a concentration of about 16 mcg. per ml., in 1-cm. cells, at the maximum at about 302 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_7H_7NO_2$ in the portion of Suspension taken by the formula $12.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference

Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Salicylamide Oral Suspension in tight containers.

Suspension available—Salicylamide Oral Suspension usually available contains 65 mg. of salicylamide in each ml.

CATEGORY and DOSE—See Salicylamide.

Salicylamide Tablets

Salicylamide Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_7H_7NO_2$.

Identification—Finely powder a number of Salicylamide Tablets, equivalent to about 1 g. of salicylamide, and triturate the powder with three 25-ml. portions of ether. Filter the ether extracts through a pledget of cotton and evaporate the filtrate to dryness on a steam bath. The residue melts between 139° and 142°, page 814, and responds to the *Identification tests* under *Salicylamide,* page 627.

Disintegration, page 878—The disintegration time limit for Salicylamide Tablets is 30 minutes.

Weight variation, page 901—Salicylamide Tablets meet the requirements of the weight variation test for tablets.

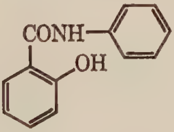
Assay—Weigh and finely powder not less than 20 Salicylamide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg. of salicylamide, to a 100-ml. beaker equipped with a mechanical stirrer and a suitable cover with a single hole for the buret tip. Proceed as directed in the *Assay* under *Salicylamide,* page 627, beginning with "Add 30 ml. of freshly neutralized dimethylformamide. . . ."

Packaging and storage—Preserve Salicylamide Tablets in well-closed containers.

Tablets available—Salicylamide Tablets usually available contain the following amounts of salicylamide: 300 and 600 mg.

CATEGORY and DOSE—See Salicylamide.

Salicylanilide



$C_{13}H_{11}NO_2$ Mol. wt. 213.24

Salicylanilide, dried at 80° for 2 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_{13}H_{11}NO_2$.

Description—Salicylanilide occurs as odorless, white or slightly pink crystals which are stable in air.

Solubility—Salicylanilide is freely soluble in alcohol, in ether, in chloroform, and in benzene. It is slightly soluble in water.

Identification—

A: Dissolve 100 mg. of Salicylanilide in 5 ml. of sodium hydroxide T.S. and pour into 100 ml. of dilute acetic acid (1 in 50) containing two drops of ferric chloride T.S.: a salmon-red precipitate forms which fades on standing. (Retain this solution for the test for *Uncombined salicylate.*)

B: Dissolve about 750 mg. of Salicylanilide in 35 ml. of glacial acetic acid and cool the solution in an ice bath, add 15 ml. of nitric acid and allow the reaction to proceed for 15 minutes, maintaining the temperature at about 8°. Collect the precipitate on a filter, wash it thoroughly with water, and recrystallize from benzene: the 5-nitrosalicylanilide so obtained melts at about 224°, page 814.

Melting range, page 814—Salicylanilide melts between 136° and 138°.

Loss on drying, page 814—Dry Salicylanilide at 80° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—The residue on ignition from 1 g. of Salicylanilide is not more than 0.05 percent.

Iron—To the residue obtained from the test for *Residue on ignition* add 1 ml. of hydrochloric acid, and evaporate to dryness. Take up the residue with 2 ml. of hydrochloric acid, dilute with 10 ml. of water, and filter if necessary to remove any insoluble particles. Finally dilute to 25.0 ml. with water. To 5.0 ml. of this solution, in a test tube, add three drops of thioglycollic acid solution (3 in 10), mix, and after a few seconds make alkaline with several drops of stronger ammonia water: any violet color present is not darker than that produced by a standard solution containing 20 mcg. of iron and treated with the same reagents in the same manner.

Uncombined salicylate—Swirl the mixture from *Identification test A* briefly and filter about 10 ml. into a test tube: the clear filtrate shows no violet color.

Assay—Transfer about 500 mg. of Salicylanilide, previously dried at 80° for 2 hours and accurately weighed, to a 125-ml. conical flask, and dissolve in 30 ml. of dimethylformamide. Add 4 drops of thymol blue T.S., and titrate with 0.1 *N* sodium methoxide, using a magnetic stirrer. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium methoxide is equivalent to 21.32 mg. of $C_{13}H_{11}NO_2$.

Packaging and storage—Preserve Salicylanilide in tight, light-resistant containers.

Category—Local antifungal.

For external use—Topically as a 3 to 5 percent ointment applied to the scalp as required.

Salicylic Acid with Zinc Oxide Paste, page 767
Saponated Cresol Solution, page 185
Secobarbital, Sodium, and Sodium Amobarbital Capsules, page 659

Selenium Sulfide

Selenium Disulfide

SeS_2 Mol. wt. 143.09

Selenium Sulfide contains not less than 52.0 percent and not more than 55.5 percent of Se (selenium).

Description—Selenium Sulfide occurs as a bright orange powder having not more than a faint odor.

Solubility—Selenium Sulfide is practically insoluble in water and in organic solvents.

Identification—

A: Digest 50 mg. of Selenium Sulfide with 5 ml. of nitric acid for 30 minutes by heating gently. Dilute to about 50 ml., filter, and to 5 ml. of the filtrate add 10 ml. of water and 5 g. of urea. Heat to boiling, cool, and add 2 ml. of potassium iodide solution (1 in 10): a yellowish orange to orange color that darkens rapidly is produced (presence of *selenium*).

B: Allow the solution obtained in *Identification test A* to stand for 10 minutes, filter, and to the filtrate add 10 ml. of barium chloride T.S.: the solution becomes turbid (presence of *sulfur*).

Residue on ignition, page 858—Selenium Sulfide yields not more than 0.2 percent of residue on ignition.

Soluble selenium compounds—Mix 10.0 g. of Selenium Sulfide with 100.0 ml. of water in a 250-ml. flask, allow to stand for 1 hour with frequent agitation, and filter. To 10.0 ml. of the filtrate add 2 ml. of 2.5 *M* formic acid, dilute to 50 ml. with water, mix, and adjust the pH, if necessary, to 2.5 ± 0.5. Add 2 ml. of freshly prepared 3,3′-diaminobenzidine hydrochloride solution (1 in 200), mix, allow to stand for 45 minutes, and then adjust the pH with ammonia T.S. to 6.5 ± 0.5. Transfer to a separator, add 10.0 ml. of toluene, shake vigorously for 1 minute, allow the layers to separate, and discard the aqueous phase. Determine the absorbance of the toluene layer in a 1-cm. cell at 420 mμ, with a suitable spectrophotometer, using a blank consisting of the same quantities of the same reagents treated in the same manner as the sample: the absorbance does not exceed that of a control prepared by treating 10.0 ml. of a solution of selenious acid (containing 0.5 mcg. of selenium in each ml.) as directed above, beginning with "To 10.0 ml. of the filtrate. . . ." (5 parts per million).

Assay—Place about 100 mg. of Selenium Sulfide, accurately weighed, in a suitable container, add 25 ml. of fuming nitric acid, and digest over gentle heat until no further solution occurs. Cool, transfer the solution to a 250-ml. volumetric flask containing 100 ml. of water, cool again, dilute to volume with water, and mix. Pipet 50.0 ml. of the solution into a small flask, add 25 ml. of water and 10 g. of urea, and heat to boiling. Cool, add 3 drops of starch T.S., and then add 10 ml. of potassium iodide solution (1 in 10), and immediately titrate with 0.05 *N* sodium thiosulfate. Perform a blank determination, and make any necessary correction. Each ml. of 0.05 *N* sodium thiosulfate is equivalent to 987.0 mcg. of Se.

Packaging and storage—Preserve Selenium Sulfide in well-closed containers.

Category—Antiseborrheic.

For external use—Topically to scalp, 5 or 10 ml. of a 2.5 percent suspension for 5 minutes, then wash off thoroughly.

Selenium Sulfide Detergent Suspension*

Selenium Sulfide Detergent Suspension is an aqueous, stabilized suspension of selenium sulfide containing a suitable dispersing agent, buffer, and detergent. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of SeS_2.

Identification—Digest about 2 g. of Selenium Sulfide Detergent Suspension with 5 ml. of nitric acid over gentle heat for 1 hour: the solution responds to the *Identification tests* under *Selenium Sulfide*, page 630, when tested as directed, beginning with "Dilute to about 50 ml. . . ."

pH, page 824—The pH of Selenium Sulfide Detergent Suspension is between 3.6 and 4.5.

Assay—Using a tared, 100-ml. volumetric flask, weigh 100 ml. of Selenium Sulfide Detergent Suspension that previously has been shaken to ensure homogeneity, allowed to stand long enough for entrapped air to rise, and finally inverted carefully just prior to transfer to the volumetric flask. Place a portion of Selenium Sulfide Detergent Suspension, equivalent to about 100 mg. of selenium sulfide, and accurately weighed, in a 125-ml. flask. Digest with 25 ml. of fuming nitric acid over gentle heat for 2 hours, and proceed as directed in the *Assay* under *Selenium Sulfide*, page 630, beginning with "Cool, transfer the solution to a 250-ml. volumetric flask." Each ml. of 0.05 *N* sodium thiosulfate is equivalent to 1.789 mg. of SeS_2. From the observed weight of 100 ml. of the Suspension, calculate the quantity of SeS_2 in each 100 ml.

Packaging and storage—Preserve in well-closed containers.

Suspension available—Selenium Sulfide Detergent Suspension usually available contains 2.5 percent of selenium sulfide.

CATEGORY and APPLICATION—See Selenium Sulfide.

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* Patented. See notice, page ii.

Senna

Senna consists of the dried leaflet of *Cassia acutifolia* Delile, known in commerce as Alexandria Senna, or of *Cassia angustifolia* Vahl, known in commerce as Tinnevelly Senna (Fam. *Leguminosæ*).

Unground Alexandria Senna occurs as inequilaterally lanceolate or lance-ovate leaflets, frequently broken; from 1.5 to 3.5 cm. in length and from 5 to 10 mm. in width, unequal at the base, with very short, stout petiolules. The leaflets are acutely cuspidate, entire, brittle, and subcoriaceous, with short and somewhat appressed hairs, few on the upper surface, more numerous on the lower surface, where they occur spreading on the midrib, especially on its lower part. The color is weak yellow to light grayish green to pale olive. The odor is characteristic and the taste mucilaginous and slightly bitter.

Unground Tinnevelly Senna occurs as usually unbroken leaflets, from 2 to 5 cm. in length and from 6 to 15 mm. in width; acute at the apex; and slightly hairy. The color of the leaves is weak yellow to pale olive.

Histology—Senna shows polygonal epidermal cells with straight walls and frequently containing mucilage; numerous, broadly elliptical stomata mostly from 20 to 35 μ in length, usually bordered by 2 neighbor-cells with their long axes parallel to that of the stoma, and rarely, though more frequently in Alexandria Senna, a third epidermal cell at the end of the stoma. The hairs are nonglandular, 1-celled, conical, often curved, with thick papillose walls, from 100 to 350 μ in length. Palisade cells in a single layer underlie both surfaces excepting in the midrib region where they occur only beneath the upper epidermis. A meristele occurs in the midrib composed of several radially arranged fibrovascular bundles, the latter separated by narrow vascular rays and supported above and below by arcs of lignified pericyclic fibers. Calcium oxalate occurs in rosette aggregates in the spongy parenchyma and in 6- to 8-sided prisms in the crystal-fibers, which lie on the outer surface of each group of pericyclic fibers.

Powdered Senna is dusky greenish yellow to light olive-brown, displaying fragments of veins bearing lignified vessels, tracheids, and crystal-fibers, isolated hairs, masses of palisade and spongy parenchyma, fragments of epidermis with stomata, free calcium oxalate rosette aggregates, and prisms from 10 to 20 μ in length. In powdered Alexandria Senna, the hairs are more numerous than in powdered Tinnevelly Senna.

Identification—Mix 500 mg. of powdered Senna with 10 ml. of an alcohol solution of potassium hydroxide (1 in 10), boil the mixture for about 2 minutes, dilute it with 10 ml. of water, and filter. Acidify the filtrate with hydrochloric acid, shake it with ether, remove the ether layer, and shake it with 5 ml. of ammonia T.S.: the latter is colored orange or bluish red.

Senna stems, pods, or other foreign organic matter, page 885—The amount of senna stems in Senna does not exceed 8 percent and the amount of senna pods or other foreign organic matter does not exceed 2 percent.

Acid-insoluble ash, page 885—Senna yields not more than 3 percent of acid-insoluble ash.

Packaging and storage—Preserve Senna against attack by insects and rodents, page 14.

CATEGORY—Cathartic.
USUAL DOSE—**2 g.**

Senna Fluidextract

Senna, in coarse powder	**1000 g.**

Prepare the Fluidextract by Process A, page 829, using a mixture of 1 volume of alcohol and 2 volumes of water as the menstruum. Macerate the drug for 24 hours, then percolate at a moderate rate, and reserve the first 800 ml. of percolate.

Alcohol content, page 772—Senna Fluidextract contains from 23 to 27 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Senna Fluidextract in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat.

CATEGORY—See Senna.
USUAL DOSE—**2 ml.**

Senna Syrup

Senna Fluidextract	**250 ml.**
Coriander Oil	**5 ml.**
Sucrose	**635 g.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Mix the coriander oil with the fluidextract, and gradually add 330 ml. of purified water. Allow the mixture to stand for 24 hours in a cool place, with occasional agitation, then filter, and pass enough purified water through the filter to obtain 580 ml. of filtrate. Dissolve the sucrose in this liquid, and add sufficient purified water to make the product measure 1000 ml. Mix well and strain.

Alcohol content, page 772—Senna Syrup contains from 5 to 7 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Senna Syrup in tight containers, preferably at a temperature not above 25°.

CATEGORY—See Senna.
USUAL DOSE—**8 ml.**

Colloidal Silicon Dioxide

SiO_2 Mol. wt. 60.08

Colloidal Silicon Dioxide is a submicroscopic fumed silica prepared by the vapor-phase hydrolysis of a silicon compound. It contains not less than 99.0 percent and not more than 100.5 percent of SiO_2, calculated on the dried basis.

Description—Colloidal Silicon Dioxide occurs as a light, white, nongritty powder of extremely fine particle size (about 15 mμ).

Solubility—Colloidal Silicon Dioxide is insoluble in water and in acids (except hydrofluoric). It is dissolved by hot solutions of alkali hydroxides.

Identification—

A: Transfer about 5 mg. of Colloidal Silicon Dioxide to a platinum crucible, and mix with about 200 mg. of anhydrous potassium carbonate. Ignite at a red heat for about 10 minutes over a burner, and cool. Dissolve the melt in 2 ml. of freshly distilled water, warming if necessary, and slowly add 2 ml. of ammonium molybdate T.S.: a deep yellow color is produced.

B: Place 1 drop of the solution obtained in *Identification test A* on a filter paper, and evaporate the solvent. Add 1 drop of a saturated solution of benzidine in glacial acetic acid, and place the paper over stronger ammonia water: a greenish blue spot is produced.

pH, page 824—The pH of a 1 in 25 dispersion of Colloidal Silicon Dioxide is between 3.5 and 4.2.

Loss on drying, page 814—Dry Colloidal Silicon Dioxide at 105° for 2 hours: it loses not more than 1 percent of its weight.

Loss on ignition—Ignite a portion of Colloidal Silicon Dioxide, previously dried at 105° for 2 hours, to constant weight in a tared platinum crucible at 1000°: it loses not more than 1 percent of its weight.

Arsenic—Transfer 2.5 g. of Colloidal Silicon Dioxide to a flask, add 50 ml. of diluted hydrochloric acid, and reflux for 30 minutes using a water condenser. Cool, filter with the aid of suction, and transfer the filtrate to a 100-ml. volumetric flask. Wash the filter and flask with several portions of hot water, and add the washings to the flask. Cool, make to volume with water, and mix: a 50.0-ml. portion of this solution, to which 3 ml. of hydrochloric acid has been added, meets the requirements of the *Arsenic Test*, page 777, omitting the addition of the dilute sulfuric acid (8 parts per million As).

Assay—Transfer about 500 mg. of Colloidal Silicon Dioxide to a tared platinum crucible, ignite at 1000° for 2 hours, cool in a desiccator, and weigh. Moisten the residue with 8 drops of alcohol and 3 drops of sulfuric acid, and then add enough hydrofluoric acid to cover the wetted sample. Evaporate to dryness on a hot plate, using medium heat (95° to 105°), then add 5 ml. of hydrofluoric acid, swirl the dish carefully to wash down the sides, and again evaporate to dryness. Ignite the dried residue to a red heat over a blast lamp, cool in a desiccator, and weigh. The difference between the total weight loss and the weight loss after ignition at 1000° represents the weight of SiO_2 in the sample taken.

Packaging and storage—Preserve Colloidal Silicon Dioxide in well-closed containers.

CATEGORY—Tablet diluent; suspending and thickening agent.

Mild Silver Protein

Mild Silver Protein is silver rendered colloidal by the presence of, or combination with, protein. It contains not less than 19.0 percent and not more than 23.0 percent of Ag (silver).

Caution: Solutions of Mild Silver Protein should be freshly prepared or contain a suitable stabilizer.

Description—Mild Silver Protein occurs as dark brown or almost black, shining scales or granules. It is odorless, is frequently hygroscopic, and is affected by light.

Solubility—Mild Silver Protein is freely soluble in water. It is practically insoluble in alcohol, in chloroform, and in ether.

Identification—

A: Heat about 100 mg. of Mild Silver Protein in a porcelain crucible until all carbonaceous matter is burned off, warm the residue with 1 ml. of nitric acid, dilute with 10 ml. of water, and add a few drops of hydrochloric acid: a white precipitate forms which dissolves in ammonia T.S.

B: Ferric chloride T.S. added to a solution of Mild Silver Protein (1 in 100) discharges the dark color and a precipitate is gradually formed.

C: To 10 ml. of a solution of Mild Silver Protein (1 in 100) add a few drops of mercuric chloride T.S.: a white precipitate is formed and the supernatant liquid becomes colorless or nearly so.

Ionic silver—To 10 ml. of a solution of Mild Silver Protein (1 in 100) add 2 ml. of a solution of sodium chloride (1 in 100): no turbidity is produced.

Distinction from strong silver protein—Dissolve 1 g. of Mild Silver Protein in 10 ml. of water. Add, all at once, 7 g. of ammonium sulfate, and stir occasionally for 30 minutes. Filter through retentive filter paper into a 50-ml. Nessler tube, returning the first portions of the filtrate to the filter, if necessary, to secure a clear filtrate, and allow the filter and precipitate to drain. Add to the clear filtrate 25 ml. of a solution of acacia (1 in 100). In a second 50-ml. Nessler tube dissolve 7 g. of ammonium sulfate in 10 ml. of water, and add to this solution 25 ml. of the solution of acacia and 1.6 ml. of 0.01 *N* silver nitrate. To each tube add 2 ml. of nitric acid, 2 ml. of diluted hydrochloric acid, and enough of the acacia solution to make the volume of each solution 50 ml. Mix the contents of each tube thoroughly, and allow to stand for 5 minutes: the turbidity of the mixture containing the sample preparation is no greater than that of the control. (Strong silver protein yields a much greater turbidity than the control.)

Assay—Ignite about 1.5 g. of Mild Silver Protein, accurately weighed, in a porcelain crucible until all of the carbon is burned off. Cool the crucible, place it in a 400-ml. beaker, and fill the crucible with dilute nitric acid (1 in 2). When the reaction has subsided, add water to immerse the crucible, cover the beaker, and heat on a steam bath until all of the silver is dissolved. Remove and rinse the crucible, and filter the solution into a conical flask. Wash the filter and residue thoroughly with water, and cool the filtrate. Add 2 ml. of ferric ammonium sulfate T.S., and titrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* ammonium thiocyanate is equivalent to 10.79 mg. of Ag.

Packaging and storage—Preserve Mild Silver Protein in tight, light-resistant containers.

CATEGORY—Local anti-infective.

APPLICATION—Topically as a 5 to 25 percent solution to the skin or mucous membrane several times a day as required.

Sitosterols

Sitosterols is a mixture of β-sitosterol (stigmast-5-en-3β-ol) ($C_{29}H_{50}O$) and related sterols of plant origin. It contains not less than 95.0 percent of total sterols and not less than 85.0 percent of unsaturated sterols, calculated on the dried basis as β-sitosterol.

Description—Sitosterols occurs as a white, essentially odorless, tasteless powder.

Solubility—Sitosterols is freely soluble in chloroform and in carbon disulfide. It is practically insoluble in water, and is slightly soluble in alcohol.

Identification—Transfer about 150 mg. of Sitosterols to a 50-ml. conical flask, add 10 ml. of pyridine and 2 ml. of benzoyl chloride, and reflux gently for 15 minutes. Cool, transfer the mixture to a separator containing 50 ml. of water, and add sodium carbonate to make it distinctly alkaline. Extract with 25 ml. of ether, wash the ether extract with 25 ml. of water, discard the washings, and evaporate the ether to dryness. Recrystallize the residue from alcohol and dry: the white crystalline benzoate derivative so obtained melts between 142° and 146°, page 814.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 10 solution of Sitosterols, previously dried at 100° for 3 hours, in carbon disulfide in the range of 3 to 12 μ exhibits maxima at the same wavelengths as that of NF Sitosterols Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Sitosterols, previously dried at 100° for 3 hours, determined in a solution in chloroform containing 200 mg. of Sitosterols in each 10 ml., is not less than $-25°$ and not more than $-38°$.

Loss on drying, page 814—Dry Sitosterols at 100° for 3 hours: it loses not more than 2 percent of its weight.

Residue on ignition, page 858—Sitosterols yields not more than 0.5 percent of residue on ignition.

Assay for unsaturated sterols (**β-sitosterol**)—Transfer to a 25-ml. glass-stoppered conical flask 500.0 mg. of Sitosterols, accurately weighed, and dissolve in 10.0 ml. of carbon disulfide. In the same manner, prepare a solution of NF Sitosterols Reference Standard having the same concentration as the sample. Concomitantly determine the absorbances of the two solutions in 0.1-mm. sodium chloride cells, at the maximum at about 9.52 μ, with a suitable infrared spectrophotometer, using carbon disulfide as the blank. Calculate the percent of unsaturated sterols, as β-sitosterol, by the formula $100 \times (A_U/A_S)$, in which A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Assay for total sterols—Transfer to a 100-ml. volumetric flask about 150 mg. of Sitosterols, accurately weighed, dilute to volume with dehydrated alcohol, and mix. Transfer 10.0 ml. of the solution to a 100-ml. beaker and heat just to boiling on a hot plate. Simultaneously heat just to boiling 9 ml. of a solution (1 in 100) of digitonin in dehydrated alcohol, and then add it to the sitosterols solution. Slowly add 2 ml. of water to the combined alcohol solutions, remove from the hot plate, cover with aluminum foil, and allow to stand overnight. Collect the precipitate in a tared sintered-glass crucible, using only gentle suction to prevent packing of the precipitate. Release the suction, then add 4 ml. of a mixture of acetone, water, and alcohol (73:18:9), and stir with a small stirring rod to suspend the precipitate. Rinse the rod with 2 ml. of the wash mixture and filter again with gentle suction. Repeat the washing procedure, using 3 ml. of the wash mixture, and dry the precipitate at 100° for 3 hours. Each g. of the precipitate is equivalent to 253 mg. of total sterols.

Packaging and storage—Preserve Sitosterols in well-closed containers.

CATEGORY—Anticholesterolemic agent.

USUAL DOSE—**3 g.** three times a day before meals.

USUAL DOSE RANGE—**9** to **30 g.** daily.

Sitosterols Suspension

Sitosterols Suspension is a suspension containing not less than 90.0 percent and not more than 110.0 percent of the labeled amount of sitosterols.

Description—Sitosterols Suspension is a white, homogeneous suspension.

Identification—Transfer an amount of Sitosterols Suspension, equivalent to about 500 mg. of sitosterols, to a separator, add 10 ml. of water, and extract with 25 ml. of chloroform. Dry the chloroform extract with anhydrous sodium sulfate, filter, and evaporate the dried chloroform solution to dryness: a portion of the residue of sitosterols so obtained responds to the *Identification test* under *Sitosterols*, page 634.

Infrared absorption—A portion of the residue obtained under *Identification* meets the requirements for *Infrared absorption* under *Sitosterols*, page 634.

Assay—Transfer to a 250-ml. separator, with the aid of 100 ml. of water, an accurately measured amount of Sitosterols Suspension, equivalent to about 5 g. of sitosterols, add 3 ml. of hydrochloric acid, and extract with 100-, 50-, and 25-ml. portions of ether, respectively. Filter the ether extracts through anhydrous sodium sulfate into a 200-ml. volumetric flask, wash the sodium sulfate and the filter with small portions of chloroform, collecting the washings in the flask, dilute to volume with chloroform, and mix. Transfer 5.0 ml. of the solution to a 100-ml. volumetric flask and evaporate to dryness on a steam bath. Dissolve the residue in dehydrated alcohol, dilute to volume with dehydrated alcohol, and mix. Transfer 10.0 ml. of this solution to a 100-ml. beaker and proceed as directed in the *Assay for total sterols* under *Sitosterols*, page 634, beginning with " . . . and heat just to boiling . . . ."

Packaging and storage—Preserve Sitosterols Suspension in well-closed containers.

Suspension available—Sitosterols Suspension usually available contains the following amount of sitosterols: 3 g. in 15 ml.

CATEGORY and DOSE—See Sitosterols.

Sodium Acetate

$CH_3COONa.3H_2O$

$C_2H_3NaO_2.3H_2O$ Mol. wt. 136.08

Sodium Acetate, dried at 80° overnight and followed by drying at 120° for 4 hours, contains not less than 99.0 percent and not more than 101.0 percent of $C_2H_3NaO_2$.

Description—Sodium Acetate occurs as colorless, transparent crystals or as a granular crystalline powder. It is odorless, or has a faint, acetous odor. It is efflorescent in warm, dry air.

Solubility—Sodium Acetate is very soluble in water and is soluble in alcohol.

Identification—

A: A solution of Sodium Acetate responds to the tests for *Sodium*, page 810, and for *Acetate*, page 807.

B: Upon ignition, Sodium Acetate yields an alkaline residue which effervesces with acids.

Loss on drying, page 814—Dry Sodium Acetate at 80° overnight and follow by drying it at 120° for 4 hours: it loses not less than 36 percent and not more than 41 percent of its weight.

Alkalinity—A solution of 2 g. of Sodium Acetate in 20 ml. of water requires not more than 0.1 ml. of 0.1 *N* sulfuric acid for neutralization, using 3 drops of phenolphthalein T.S. as the indicator.

Arsenic—A solution of 1.25 g. of Sodium Acetate in water meets the requirements of the *Arsenic Test*, page 777 (8 parts per million As).

Heavy metals, page 806—Dissolve 1 g. of Sodium Acetate in 1 ml. of 1 *N* hydrochloric acid and enough water to make 25 ml., and continue as directed for *Solution B* under *Method I*, page 806, except use glacial acetic acid to adjust the pH: the heavy metals limit for Sodium Acetate is 10 parts per million.

Potassium compounds—Mix a few drops of sodium bitartrate T.S. with about 5 ml. of a clear, saturated solution of Sodium Acetate: no turbidity is produced.

Assay—Weigh accurately about 200 mg. of Sodium Acetate, previously dried at 80° overnight and followed by drying at 120° for 4 hours, and dissolve it in 25 ml. of glacial acetic acid, warming gently if necessary to effect complete solution. Add 2 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 8.203 mg. of $C_2H_3NaO_2$.

Packaging and storage—Preserve Sodium Acetate in tight containers.

Category—Alkalizer (systemic and urinary).

Usual dose—**1.5 g.**

Sodium Alginate

Sodium Alginate is the purified carbohydrate product extracted from brown seaweeds by the use of dilute alkali. It consists chiefly of the sodium salt of alginic acid, a polyuronic acid composed of beta D-mannuronic acid residues linked so that the carboxyl group of each unit is free while the aldehyde group is shielded by a glycosidic linkage.

Description—Sodium Alginate occurs as a nearly odorless and tasteless, coarse or fine powder, yellowish white in color.

Solubility—Sodium Alginate dissolves in water, forming a viscous, colloidal solution. It is insoluble in alcohol and in hydroalcoholic solutions in which the alcohol content is greater than about 30 percent by weight. It is insoluble in chloroform, in ether, and in acids when the pH of the resulting solution becomes lower than about 3.

Identification—

A: To 5 ml. of a solution of Sodium Alginate (1 in 100) add 1 ml. of calcium chloride T.S.: a voluminous gelatinous precipitate is formed immediately.

B: To 10 ml. of a solution of Sodium Alginate (1 in 100) add 1 ml. of diluted sulfuric acid: a heavy gelatinous precipitate is formed.

Loss on drying, page 814—Dry Sodium Alginate at 105° for 4 hours: it loses not more than 15 percent of its weight.

Ash, page 885—Sodium Alginate yields not less than 18 percent and not more than 24 percent of ash, taking care to heat at a temperature not exceeding a dull red heat.

Water-insoluble substances—Dissolve 500 mg. of Sodium Alginate in 200 ml. of boiling water in a covered beaker and heat on a steam bath for 1 hour with frequent stirring. Without cooling, filter the solution through a tared filtering crucible with an asbestos mat. Wash the filter thoroughly with hot water, dry at 105° for 1 hour, cool, and weigh. The weight of insoluble matter does not exceed 1 mg.

Arsenic—A *Test Preparation* prepared with 6.67 g. of Sodium Alginate, as directed for organic compounds, meets the requirements of the *Arsenic Test*, page 777 (1.5 parts per million As).

Lead—Add 1.0 g. of Sodium Alginate to 20 ml. of nitric acid in a 250-ml. conical flask, mix well, and heat carefully until the Sodium Alginate is dissolved. Continue the heating until the volume is reduced to about 7 ml. Cool rapidly to room temperature, transfer to a 100-ml. volumetric flask and dilute to volume with water. A 50.0-ml. portion of this solution contains not more than 5 mcg. of lead (corresponding to not more than 10 parts per million) when tested according to the *Lead Limit Test*, page 813, using 15 ml. of ammonium citrate solution, 3 ml. of potassium cyanide solution, and 0.5 ml. of hydroxylamine hydrochloride solution. After the first dithizone extractions, wash the combined chloroform layers with 5 ml. of water, discarding the water layer and continuing in the usual manner by extracting with 20 ml. of 1 percent nitric acid.

Starch—To 5 ml. of a solution of Sodium Alginate (1 in 1000) add 1 drop of iodine T.S.: not even a transient blue color is produced.

Gelatin—To 5 ml. of a solution of Sodium Alginate (1 in 100) add 1 ml. of a solution of ammonium molybdate (1 in 20): no precipitate is formed within 5 minutes.

Packaging and storage—Preserve Sodium Alginate in tight containers.

Category—Suspending agent.

Sodium Amobarbital and Sodium Secobarbital Capsules, page 659

Sodium Biphosphate

Sodium Dihydrogen Phosphate

$NaH_2PO_4.H_2O$ Mol. wt. 137.99

Sodium Biphosphate contains not less than 98.0 percent and not more than 103.0 percent of NaH_2PO_4, calculated on the anhydrous basis.

Description—Sodium Biphosphate occurs as colorless crystals or as a white, crystalline powder. It is odorless and is slightly deliquescent. Its solutions are acid to litmus and effervesce with sodium carbonate.

Solubility—Sodium Biphosphate is freely soluble in water. It is practically insoluble in alcohol.

Identification—A solution of Sodium Biphosphate (1 in 20) responds to the tests for *Sodium*, page 810, and for *Phosphate*, page 809.

Water, page 900—Determine the water content of Sodium Biphosphate by the titrimetric method (*Residual Titration* procedure): not less than 10 percent and not more than 15 percent is found.

Free acid and disodium phosphate—Dissolve 2 g. of Sodium Biphosphate in 40 ml. of water, and add 1 drop of methyl orange T.S. If the solution is pink, it requires the addition of not more than 0.3 ml. of 1 *N* sodium hydroxide to change it to yellow. If the solution is yellow, it requires the addition of not more than 0.3 ml. of 1 *N* sulfuric acid to render it pink.

Chloride, page 784—One g. of Sodium Biphosphate shows no more chloride than corresponds to 0.2 ml. of 0.02 *N* hydrochloric acid (0.014 percent).

Sulfate, page 784—A 200-mg. portion of Sodium Biphosphate shows no more sulfate than corresponds to 0.3 ml. of 0.02 *N* sulfuric acid (0.15 percent).

Aluminum, calcium, etc.—A solution of Sodium Biphosphate (1 in 10) does not become turbid when rendered slightly alkaline to litmus paper with ammonia T.S.

Arsenic—A solution of 1.25 g. of Sodium Biphosphate in water meets the requirements of the *Arsenic test*, page 777 (8 parts per million As).

Heavy metals, page 806—Dissolve 1 g. of Sodium Biphosphate in 20 ml. of water, and add 1 ml. of diluted hydrochloric acid and water to make 25 ml.: the heavy metals limit for Sodium Biphosphate is 20 parts per million.

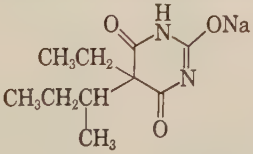
Assay—Dissolve about 2.5 g. of Sodium Biphosphate, accurately weighed, in 10 ml. of cold water, add 20 ml. of a cold, saturated solution of sodium chloride, then add phenolphthalein T.S., and titrate with 1 *N* sodium hydroxide, keeping the temperature of the solution between 10° and 15° during the entire titration. Perform a blank determination, and make any necessary correction. Each ml. of 1 *N* sodium hydroxide is equivalent to 120.0 mg. of NaH_2PO_4.

Packaging and storage—Preserve Sodium Biphosphate in well-closed containers.

CATEGORY—Acidifier (urinary).
USUAL DOSE—**600 mg.** four times a day.
USUAL DOSE RANGE—**500 mg.** to **1 g.** one to six times a day.

Sodium Biphosphate and Methenamine Tablets, page 434

Sodium Butabarbital



Sodium 5-*sec*-Butyl-5-ethylbarbiturate

$C_{10}H_{15}N_2NaO_3$ Mol. wt. 234.23

Sodium Butabarbital contains not less than 98.2 percent and not more than 100.5 percent of $C_{10}H_{15}N_2NaO_3$, calculated on the dried basis.

Description—Sodium Butabarbital occurs as a white, bitter powder.

Solubility—Sodium Butabarbital is freely soluble in water and in alcohol. It is practically insoluble in benzene and in absolute ether.

Identification—

A: Ignite 100 mg. of Sodium Butabarbital: the residue responds to the tests for *Carbonate*, page 808, and for *Sodium*, page 810.

B: Dissolve 300 mg. of Sodium Butabarbital in 10 ml. of water, and divide it into two portions. To one portion add 1 ml. of mercuric chloride T.S.: a white precipitate forms which is soluble in an excess of stronger ammonia water. To the other portion add 5 ml. of silver nitrate T.S.: a white precipitate forms which is soluble in an excess of stronger ammonia water.

C: The residue of butabarbital obtained in the *Assay* melts between 164° and 167°, page 814.

pH, page 824—The pH of a solution of Sodium Butabarbital (1 in 100) is between 9.0 and 10.2.

Loss on drying, page 814—Dry Sodium Butabarbital at 105° for 4 hours: it loses not more than 5 percent of its weight.

Heavy metals, page 806—Dissolve 1 g. of Sodium Butabarbital in 21 ml. of water and add slowly, with stirring, 4 ml. of 1 *N* hydrochloric acid, filter, and dilute the filtrate to 25 ml. with water: the heavy metals limit for Sodium Butabarbital is 30 parts per million.

Free butabarbital—Place about 1 g. of Sodium Butabarbital, accurately weighed, in a glass-stoppered cylinder, add 50 ml. of benzene, stopper, and shake the mixture for 10 minutes. Decant the supernatant liquid through filter paper into a tared beaker, and repeat the extraction twice, using 25 ml. and 15 ml. of benzene, respectively, and the same filter. Carefully evaporate the combined filtrates to dryness, and dry the residue at 105° for 30 minutes: the weight of the residue does not exceed 0.6 percent of the weight of Sodium Butabarbital taken.

Assay—Dissolve about 500 mg. of Sodium Butabarbital, accurately weighed, in 10 ml. of water in a separator. Add 15 ml. of diluted hydrochloric acid, and proceed as directed under *Barbiturate Assay*, page 781, beginning with "Completely extract the liberated . . . ," using seven portions of chloroform of 25, 20, 20, 15, 15, 15, and 15 ml., respectively. Omit the final addition of 10 ml. of ether and re-evaporation. The weight of the dried butabarbital, multiplied by 1.104, represents the weight of $C_{10}H_{15}N_2NaO_3$ in the Sodium Butabarbital taken.

Packaging and storage—Preserve Sodium Butabarbital in tight containers.

CATEGORY—Sedative.

USUAL DOSE—Sedative, **15** to **30 mg.** three or four times a day; hypnotic, **100 mg.**

USUAL DOSE RANGE—Sedative, **7.5** to **60 mg.**; hypnotic, **100** to **200 mg.**

Sodium Butabarbital Capsules

Sodium Butabarbital Capsules contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{15}N_2NaO_3$.

Identification—

A: The filtrate from a water suspension of the contents of Sodium Butabarbital Capsules responds to *Identification test B* under *Sodium Butabarbital*, page 637.

B: The residue of butabarbital obtained in the *Assay* melts between 164° and 167°, page 814.

Content uniformity, *Method II*, page 798—Sodium Butabarbital Capsules meet the requirements of the content uniformity test for capsules, using the following special procedure:

Standard preparation—Transfer about 50 mg. of NF Sodium Butabarbital Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add a mixture of 1 *N* hydrochloric acid in methanol (1 in 10) to volume, and mix.

Test preparation—Quantitatively transfer the contents of one capsule to a 25-ml. volumetric flask, add a mixture of 1 *N* hydrochloric acid in methanol (1 in 10) to volume, and mix. Filter, discarding the first 5 ml. of filtrate, and dilute the subsequent filtrate quantitatively and stepwise, if necessary, with the hydrochloric acid-methanol mixture to provide a solution containing 500 to 600 mcg. of sodium butabarbital per ml.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 100-ml. volumetric flasks, and transfer 2.0 ml. of a mixture of 1 *N* hydrochloric acid in methanol (1 in 10) to a third 100-ml. volumetric flask to serve as a blank. Dilute each flask to volume with pH 9.6 alkaline borate buffer, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 240 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Stan-*

dard preparation as A_S and that from the *Test preparation* as A_U. Calculate the quantity, in mg., of $C_{10}H_{15}N_2NaO_3$ in the capsule by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of sodium butabarbital in the capsule; D is the exact concentration, in mcg. per ml., of sodium butabarbital in the *Test preparation*, based upon the labeled quantity per capsule and the extent of dilution; and C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Assay—Weigh the contents of not less than 20 Sodium Butabarbital Capsules, and mix the powder. Proceed as directed under *Barbiturate Assay*, page 781. Complete extraction of the liberated butabarbital is usually obtained with seven portions of chloroform of 25, 20, 20, 15, 15, 15, and 15 ml., respectively. Omit the final addition of 10 ml. of ether and re-evaporation. The weight of the residue, multiplied by 1.104, represents the weight of $C_{10}H_{15}N_2NaO_3$ in the portion of the Capsules taken.

Packaging and storage—Preserve Sodium Butabarbital Capsules in well-closed containers.

Capsules available—Sodium Butabarbital Capsules usually available contain the following amounts of sodium butabarbital: 15, 30, 50, and 100 mg.

CATEGORY and DOSE—See Sodium Butabarbital.

Sodium Butabarbital Elixir

Sodium Butabarbital Elixir contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{15}N_2NaO_3$.

Identification—The butabarbital obtained in the *Assay*, when recrystallized from hot alcohol and dried at 105° for 30 minutes, melts between 164° and 167°, page 814.

Assay—Pipet into a separator an accurately measured volume of Sodium Butabarbital Elixir, equivalent to about 150 mg. of sodium butabarbital, make it distinctly alkaline by the addition of sodium hydroxide T.S., and saturate it with sodium chloride. Extract the mixture with two 15-ml. portions of ether, and discard the ether. Acidify the solution with hydrochloric acid and make it just alkaline to litmus by adding small portions of sodium bicarbonate (carbonate-free). Proceed as directed under *Barbiturate Assay*, page 781, beginning with "Completely extract the liberated . . . ," using 20-ml. portions of chloroform. Omit the final addition of 10 ml. of ether and re-evaporation. The weight of the dried butabarbital, multiplied by 1.104, represents the weight of $C_{10}H_{15}N_2NaO_3$ in the portion of the Elixir taken.

Alcohol content, page 772—Sodium Butabarbital Elixir contains not less than 95 percent and not more than 115 percent of the labeled amount of C_2H_5OH.

Packaging and storage—Preserve Sodium Butabarbital Elixir in tight containers.

Elixir available—Sodium Butabarbital Elixir usually available contains the following amount of sodium butabarbital: 30 mg. per 5 ml.

CATEGORY and DOSE—See Sodium Butabarbital.

Sodium Butabarbital Tablets

Sodium Butabarbital Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{15}N_2NaO_3$.

Identification—

A: Digest a quantity of finely powdered Sodium Butabarbital Tablets, equivalent to 500 mg. of sodium butabarbital, with 20 ml. of water, and filter, if necessary. A 10-ml. portion of the filtrate responds to *Identification test B* under *Sodium Butabarbital*, page 637.

B: The residue of butabarbital obtained in the *Assay* melts between 164° and 167°, page 814.

Disintegration, page 878—The disintegration time limit for Sodium Butabarbital Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Sodium Butabarbital Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure:

Standard preparation—Transfer about 50 mg. of NF Sodium Butabarbital Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add a mixture of 1 *N* hydrochloric acid in methanol (1 in 10) to volume, and mix.

Test preparation—Quantitatively transfer a finely powdered tablet to a 25-ml. volumetric flask, add a mixture of 1 *N* hydrochloric acid in methanol (1 in 10) to volume, and mix. Filter, discarding the first 5 ml. of filtrate, and dilute the subsequent filtrate quantitatively and stepwise, if necessary, with the hydrochloric acid-methanol mixture to provide a solution containing 500 to 600 mcg. of sodium butabarbital per ml.

Procedure—Transfer 2.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 100-ml. volumetric flasks, and transfer 2.0 ml. of a mixture of 1 *N* hydrochloric acid in methanol (1 in 10) to a third 100-ml. volumetric flask to serve as a blank. Dilute each flask to volume with pH 9.6 alkaline borate buffer, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 240 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Test preparation* as A_U. Calculate the quantity, in mg., of $C_{10}H_{15}N_2NaO_3$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of sodium butabarbital in the tablet; D is the exact concentration, in mcg. per ml., of sodium butabarbital in the *Test preparation*, based upon the labeled quantity per tablet and the extent of dilution; and C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Assay—Weigh and finely powder not less than 20 Sodium Butabarbital Tablets. Proceed as directed under *Barbiturate Assay*, page 781. Complete extraction of the liberated butabarbital is usually obtained with seven portions of chloroform of 25, 20, 20, 15, 15, 15, and 15 ml., respectively. Omit the final addition of 10 ml. of ether and re-evaporation. The weight of the residue, multiplied by 1.104, represents the weight of $C_{10}H_{15}N_2NaO_3$ in the portion of the Tablets taken.

Packaging and storage—Preserve Sodium Butabarbital Tablets in well-closed containers.

Tablets available—Sodium Butabarbital Tablets usually available contain the following amounts of sodium butabarbital: 15, 30, 50, and 100 mg.

CATEGORY and DOSE—See Sodium Butabarbital.

Sodium Carboxymethylcellulose Tablets

Sodium Carboxymethylcellulose Tablets contain an amount of Na (sodium) equivalent to not less than 6.8 percent and not more than 8.6 percent of the labeled amount of sodium carboxymethylcellulose.

Identification—Digest a quantity of powdered Sodium Carboxymethylcellulose Tablets, equivalent to about 1 g. of sodium carboxymethylcellulose, with 50 ml. of water until solution is virtually complete, and filter: the filtrate responds to the following tests:

A: To about 30 ml. of the solution add 3 ml. of hydrochloric acid: a white precipitate is formed.

B: To the remainder of the solution add an equal volume of barium chloride T.S.: a fine, white, precipitate is formed.

C: The filtrate from *Identification test A* responds to the tests for *Sodium*, page 810.

Disintegration, page 878—The disintegration time limit for Sodium Carboxymethylcellulose Tablets is 2 hours.

Weight variation, page 901—Sodium Carboxymethylcellulose Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Sodium Carboxymethylcellulose Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg. of sodium carboxymethylcellulose, add 80 ml. of glacial acetic acid, heat the mixture on a steam bath for 20 minutes, cool to room temperature, and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 2.299 mg. of Na.

Packaging and storage—Preserve Sodium Carboxymethylcellulose Tablets in tight containers.

Tablets available—Sodium Carboxymethylcellulose Tablets usually available contain the following amount of sodium carboxymethylcellulose: 500 mg.

CATEGORY—Cathartic.

USUAL DOSE OF SODIUM CARBOXYMETHYLCELLULOSE—**1.5 g.** three times a day with meals.

Sodium Chloride and Dextrose Tablets

Sodium Chloride and Dextrose Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of NaCl (sodium chloride) and of $C_6H_{12}O_6.H_2O$ (dextrose).

Identification—

A: A filtered solution of Sodium Chloride and Dextrose Tablets responds to the tests for *Sodium*, page 810, and for *Chloride*, page 808.

B: Add a few drops of the filtered solution of Sodium Chloride and Dextrose Tablets to 5 ml. of hot alkaline cupric tartrate T.S.: a copious red precipitate of cuprous oxide is formed.

Disintegration, page 878—The disintegration time limit for Sodium Chloride and Dextrose Tablets is 30 minutes.

Weight variation, page 901—Sodium Chloride and Dextrose Tablets meet the requirements of the weight variation test for tablets.

Assay for dextrose—Dissolve not less than 10 Sodium Chloride and Dextrose Tablets, containing from 2 to 5 g. of dextrose, in about 75 ml. of water in a 100-ml. volumetric flask, add several drops of ammonia T.S., dilute to volume, and mix. After 30 minutes filter through a dry filter and determine the angular rotation in a 200-mm. tube at 25°, retaining the excess of the solution for the *Assay for sodium chloride*. The observed rotation in degrees, multiplied by 1.0425, represents the weight, in g., of $C_6H_{12}O_6.H_2O$ in the sample taken.

Assay for sodium chloride—Dilute 20.0 ml. of the solution used for the *Assay for dextrose* to 100.0 ml. with water. Transfer an accurately measured portion, equivalent to about 250 mg. of sodium chloride, to a glass-stoppered flask, and dilute with water to make 50 ml. Add 50.0 ml. of 0.1 *N* silver nitrate, 3 ml. of nitric acid, 3 ml. of nitrobenzene, and 2 ml. of ferric ammonium sulfate T.S. Shake well, and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 5.844 mg. of NaCl.

Packaging and storage—Preserve Sodium Chloride and Dextrose Tablets in well-closed containers.

Tablets available—Sodium Chloride and Dextrose Tablets usually available contain the following amounts of sodium chloride and dextrose, of each: 200 and 450 mg.

CATEGORY—Electrolyte and nutrient replenisher.

Sodium Chloride and Fructose Injection, page 321

Sodium Chlorothiazide for Injection

Sodium Chlorothiazide for Injection is a sterile mixture of sodium chlorothiazide and mannitol. It contains $C_7H_5ClN_3NaO_4S_2$ (sodium chlorothiazide) equivalent to not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_7H_6ClN_3O_4S_2$ (chlorothiazide).

Identification—

A: Fuse an amount of Sodium Chlorothiazide for Injection, equivalent to about 100 mg. of chlorothiazide, with a pellet of sodium hydroxide: the ammonia fumes produced turn moistened red litmus paper blue. The fusion mixture responds to the test for *Sulfite*, page 810.

B: The ultraviolet absorption spectrum of the solution prepared for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of a 1 in 100,000 solution of NF Chlorothiazide Reference Standard in 0.1 *N* sodium hydroxide, similarly measured.

pH, page 824—The pH of a solution of Sodium Chlorothiazide for Injection, prepared as directed in its labeling, is between 9.2 and 10.0.

Weight variation, page 901—Sodium Chlorothiazide for Injection meets the requirements of the weight variation test for sterile solids.

Other requirements—Sodium Chlorothiazide for Injection meets the requirements under *Injections*, page 810.

Assay—Transfer an accurately weighed portion of Sodium Chlorothiazide for Injection, equivalent to about 500 mg. of chlorothiazide, to a 1000-ml. volumetric flask, add 0.1 *N* sodium hydroxide to volume, and mix. Transfer 5.0 ml. of this solution to a 250-ml. volumetric flask, dilute to volume with 0.1 *N* sodium hydroxide, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Chlorothiazide Reference Standard, in the same medium at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 292 mμ, with a suitable spectrophotometer, using 0.1 N sodium hydroxide as the blank. Calculate the quantity, in mg., of $C_7H_6ClN_3O_4S_2$ in the sample taken by the formula $50C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Sodium Chlorothiazide for Injection in containers for Sterile Solids as described under *Injections*, page 810.

Size available—Sodium Chlorothiazide for Injection usually available contains sodium chlorothiazide equivalent to the following amount of chlorothiazide: 500 mg.

CATEGORY and DOSE—See Chlorothiazide.

Anticoagulant Sodium Citrate Solution

Anticoagulant Sodium Citrate Solution is a sterile solution of sodium citrate in water for injection and contains, in each 100 ml., not less than 3.80 g. and not more than 4.20 g. of $C_6H_5Na_3O_7.2H_2O$. It contains no bacteriostatic agents.

Sodium Citrate (dihydrate)........................	**40 g.**
Water for Injection, a sufficient quantity, to make......	**1000 ml.**

NOTE—Anhydrous sodium citrate (35.1 g.) may be used instead of the dihydrate.

Dissolve the sodium citrate in sufficient water for injection to make 1000 ml., and filter until clear. Place the solution in suitable containers, and sterilize.

Description—Anticoagulant Sodium Citrate Solution is clear and colorless.

Identification—When evaporated to a concentration of 1 in 20, Anticoagulant Sodium Citrate Solution responds to the tests for *Sodium*, page 810, and for *Citrate*, page 808.

pH, page 824—The pH of Anticoagulant Sodium Citrate Solution is between 6.4 and 7.5.

Pyrogen—When diluted with pyrogen-free saline T.S. to contain approximately 0.5 percent of sodium citrate, Anticoagulant Sodium Citrate Solution meets the requirements of the *Pyrogen Test*, page 851.

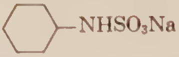
Other requirements—Anticoagulant Sodium Citrate Solution meets the requirements under *Injections*, page 810.

Assay—Pipet 10.0 ml. of Anticoagulant Sodium Citrate Solution into a 250-ml. beaker, and evaporate to dryness. Add 100 ml. of glacial acetic acid, stir until completely dissolved, and titrate with 0.1 N perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Each ml. of 0.1 N perchloric acid is equivalent to 9.803 mg. of $C_6H_5Na_3O_7.2H_2O$.

Packaging and storage—Preserve Anticoagulant Sodium Citrate Solution in single-dose containers, preferably of Type I or Type II glass.

CATEGORY—Anticoagulant for plasma and for blood for fractionation.

Sodium Cyclamate



Sodium Cyclohexanesulfamate

$C_6H_{12}NNaO_3S$ Mol. wt. 201.22

Sodium Cyclamate, dried at 105° for 1 hour, contains not less than 98.0 percent and not more than 101.0 percent of $C_6H_{12}NNaO_3S$.

Description—Sodium Cyclamate occurs as white crystals or as a white, crystalline powder. It is odorless. Sodium Cyclamate in dilute solution is about 30 times as sweet as sucrose. Its solutions are neutral to litmus.

Solubility—Sodium Cyclamate is freely soluble in water and is soluble in propylene glycol. It is practically insoluble in alcohol, in chloroform, and in ether.

Identification—

A: To 10 ml. of a solution of Sodium Cyclamate (1 in 100) add 1 ml. of hydrochloric acid and then add 1 ml. of barium chloride T.S.: the solution remains clear. Add 1 ml. of sodium nitrite solution (1 in 10): a white precipitate forms.

B: A solution of Sodium Cyclamate responds to the tests for *Sodium*, page 810.

Loss on drying, page 814—Dry Sodium Cyclamate at 105° for 1 hour: it loses not more than 1 percent of its weight.

Arsenic—A *Test Preparation* prepared with 3.33 g. of Sodium Cyclamate, as directed for organic compounds, meets the requirements of the *Arsenic Test*, page 777 (3 parts per million As).

Selenium—A *Test Preparation* prepared with 200 mg. of Sodium Cyclamate meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Cyclohexylamine—

Alkaline disodium edetate solution—Mix 100 g. of disodium edetate with 400 ml. of water, add 340 ml. of sodium hydroxide solution (1 in 10), dilute to 1000 ml. with water, and mix to dissolve.

Methyl orange-boric acid solution—Dissolve 200 mg. of methyl orange and 3.5 g. of boric acid in 100 ml. of water, heating on a steam bath to effect solution. Allow to stand for at least 24 hours, and filter before use.

Standard preparation—Transfer 100.0 mg. of cyclohexylamine to a 100-ml. volumetric flask, dissolve in 50 ml. of water and 0.5 ml. of hydrochloric acid, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with water, and mix. Transfer 5.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with water, and mix.

Test preparation—Transfer 10.0 g. of Sodium Cyclamate to a 100-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix.

Procedure—Transfer 10.0 ml. each of the *Standard preparation* and of the *Test preparation* to separate 50-ml. glass-stoppered centrifuge tubes, and transfer 10.0 ml. of water to a third tube to serve as a blank. To each tube add 3.0 ml. of *Alkaline disodium edetate solution* and 15.0 ml. of a 20:1 mixture of chloroform and *n*-butanol, shake the tubes for 2 minutes, and centrifuge. Remove and discard the aqueous layer in each tube, and then transfer 10.0 ml. of the chloroform solution from each tube to separate centrifuge tubes. To each tube add 2.0 ml. of *Methyl orange-boric acid solution*, shake the tubes for 2 minutes, and centrifuge. Remove and discard the aqueous layer in each tube, then add to each tube 1 g. of anhydrous sodium sulfate, shake well, and allow to settle. Transfer 5.0 ml. of each clear chloroform solution to separate test tubes, add 0.5 ml. of a 50:1 mixture of methanol and sulfuric acid, and mix. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 520 mμ, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance of the solution from the *Test preparation* does not exceed that from the *Standard preparation*, corresponding to not more than 25 parts per million of cyclohexylamine.

Dicyclohexylamine—

Reagent solution A—To about 60 ml. of water add 75 mg. of bromophenol blue followed by 10 ml. of 0.1 *M* sodium bicarbonate, and stir without heating until solution is complete. Adjust the pH to 4.0 with 0.2 *N* hydrochloric acid, dilute to 100 ml. with water, and mix. Store in a cool, dark place and do not use after 48 hours.

Reagent solution B—Mix 200 ml. of 1 *N* hydrochloric acid with 166 ml. of glacial acetic acid, dilute to 1000 ml. with water, and mix.

Procedure—Transfer 10.0 g. of Sodium Cyclamate to a separator, dissolve in 100 ml. of water, add 10 ml. of sodium hydroxide T.S., and extract with one 10-ml. portion and two 5-ml. portions of chloroform, combining the extracts in a second separator. To the second separator add 100 ml. of water, 3.0 ml. of *Reagent solution B*, and 1.0 ml. of *Reagent solution A*, then shake the mixture for 3 minutes, and allow to stand for 30 minutes protected from direct sunlight. Quantitatively transfer the chloroform layer to a 25-ml. volumetric flask, dilute to volume with chloroform, and mix. Determine the absorbance of this solution in a 5-cm. cell, at the maximum at about 410 mμ, with a suitable spectrophotometer, using chloroform as the blank. Concomitantly determine the absorbance of a reagent blank prepared with the same quantities of the same reagents, omitting only the test sample: the difference between the absorbance of the solution from the sample and that of the reagent blank is not greater than 0.075, indicating no measurable quantity of dicyclohexylamine in the sample.

Heavy metals, page 806—Dissolve 1 g. of Sodium Cyclamate in 25 ml. of water: the heavy metals limit for Sodium Cyclamate is 10 parts per million.

Assay—Dissolve about 400 mg. of Sodium Cyclamate, previously dried at 105° for 1 hour and accurately weighed, in 50 ml. of water and 5 ml. of hydrochloric acid. Titrate the solution at room temperature with 0.1 *M* sodium nitrite. Add the last ml. of titrant dropwise until a blue color is produced immediately when the titrated solution is spotted on starch iodide test paper. When the titration is complete, the end-point is reproducible after the mixture has been allowed to stand for 1 minute. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 20.12 mg. of $C_6H_{12}NNaO_3S$.

Packaging and storage—Preserve Sodium Cyclamate in well-closed containers.

CATEGORY—Non-nutritive sweetener.

Sodium Cyclamate and Sodium Saccharin Solution*

Sodium Cyclamate and Sodium Saccharin Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_6H_{12}NNaO_3S$ (sodium cyclamate) and of $C_7H_4NNaO_3S.2H_2O$ (sodium saccharin). The labeled concentration of sodium cyclamate is not less than 6.0 percent, and is at least 10 times the labeled concentration of sodium saccharin.

Description—Sodium Cyclamate and Sodium Saccharin Solution is a clear, colorless liquid having a sweet taste.

Identification—

A: Dilute 1 ml. of Sodium Cyclamate and Sodium Saccharin Solution with water to 10 ml., acidify with hydrochloric acid, and add 1 ml. of barium chloride T.S.: the solution remains clear. Add 1 ml. of sodium nitrite solution (1 in 10): a white precipitate forms (*presence of cyclamate*).

B: Evaporate 15 ml. of Sodium Cyclamate and Sodium Saccharin Solution to dryness, dissolve the residue in 5 ml. of sodium hydroxide solution (1 in 20), evaporate the solution to dryness, and gently fuse the residue over a small flame until it no longer evolves ammonia. Allow the residue to cool, dissolve it in 20 ml. of water, neutralize the solution with diluted hydrochloric acid, and filter: the addition of a drop of ferric chloride T.S. to the filtrate produces a violet color.

C: Sodium Cyclamate and Sodium Saccharin Solution responds to the tests for *Sodium*, page 810.

Assay for sodium cyclamate—Transfer an accurately measured volume of Sodium Cyclamate and Sodium Saccharin Solution, equivalent to about 500 mg. of sodium cyclamate, into a 250-ml. beaker, and add about 50 ml. of water and 5 ml. of hydrochloric acid. Proceed as directed in the *Assay* under *Sodium Cyclamate*, page 642, beginning with "Titrate the solution at room temperature . . . ."

Assay for sodium saccharin—Transfer an accurately measured volume of Sodium Cyclamate and Sodium Saccharin Solution, equivalent to about 150 mg. of sodium saccharin, into a 250-ml. separator, add 25 ml. of diluted hydrochloric acid, and extract with three 50-ml. portions of ether. Wash the combined ether extracts with 5 ml. of water, and discard the washing. Evaporate the extract to about 5 ml., transfer to a platinum crucible with the aid of small portions of ether, and evaporate to dryness on a steam bath. Add about 3 ml. of sodium carbonate T.S., rotate the crucible to bring the solution in complete contact with the residue, and evaporate to dryness on a steam bath. To the residue add 2 g. each of anhydrous sodium carbonate and anhydrous potassium carbonate, heat gently at first and then to complete fusion for 30 minutes. Cool, dissolve the fused mass in water, add 5 ml. of bromine T.S., acidify with hydrochloric acid, and filter through paper into a beaker. Wash the crucible and the filter with water, collecting the washings in the beaker. Dilute the combined filtrate and washings to 200 ml. with water, heat to boiling, and gradually add, in small portions at a time and while constantly stirring, an excess of hot barium chloride T.S. Heat the mixture on a steam bath for 1 hour or until the supernatant liquid is clear, collect the precipitate of barium sulfate on a tared porcelain filter crucible, wash until free from chloride, dry, ignite, and weigh. The weight of barium sulfate so obtained, multiplied by 1.033, represents the weight of $C_7H_4NNaO_3S.2H_2O$ in the portion of the Solution taken.

Packaging and storage—Preserve Sodium Cyclamate and Sodium Saccharin Solution in tight containers.

CATEGORY—See Sodium Cyclamate.

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* Patented. See notice, page ii.

Sodium Cyclamate and Sodium Saccharin Tablets*

Sodium Cyclamate and Sodium Saccharin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_6H_{12}NNaO_3S$ (sodium cyclamate) and of $C_7H_4NNaO_3S.2H_2O$ (sodium saccharin). The labeled content of sodium cyclamate is at least 10 times the labeled content of sodium saccharin.

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* Patented. See notice, page ii.

Identification—

A: Dissolve 4 Sodium Cyclamate and Sodium Saccharin Tablets in 20 ml. of water: the solution responds to *Identification tests A* and *C* under *Sodium Cyclamate and Sodium Saccharin Solution*, page 644.

B: Dissolve 20 Sodium Cyclamate and Sodium Saccharin Tablets in 20 ml. of water in a 250-ml. separator, add 25 ml. of diluted hydrochloric acid, and extract with three 50-ml. portions of ether. Wash the combined ether extracts with 5 ml. of water, discard the washing, and evaporate the ether to dryness. Dissolve the residue in 5 ml. of sodium hydroxide solution (1 in 20), evaporate the solution to dryness, and gently fuse the residue over a small flame until it no longer evolves ammonia. Allow the residue to cool, dissolve it in 20 ml. of water, neutralize the solution with diluted hydrochloric acid, and filter: the addition of a drop of ferric chloride T.S. to the filtrate produces a violet color.

Solubility—Place 5 Sodium Cyclamate and Sodium Saccharin Tablets in a 250-ml. beaker containing 150 ml. of water at 25°. Stir the mixture for 5 minutes: all of the tablets dissolve.

Weight variation, page 901—Sodium Cyclamate and Sodium Saccharin Tablets meet the requirements of the weight variation test for tablets.

Assay for sodium cyclamate—Weigh and finely powder not less than 20 Sodium Cyclamate and Sodium Saccharin Tablets. Weigh accurately a portion of the powder, equivalent to about 400 mg. of sodium cyclamate, transfer to a 250-ml. beaker, and dissolve in 50 ml. of water and 5 ml. of hydrochloric acid. Proceed as directed in the *Assay* under *Sodium Cyclamate*, page 642, beginning with "Titrate the solution at room temperature . . . ."

Assay for sodium saccharin—Dissolve 20 Sodium Cyclamate and Sodium Saccharin Tablets in 20 ml. of water in a 250-ml. separator. Proceed as directed in the *Assay for sodium saccharin* under *Sodium Cyclamate and Sodium Saccharin Solution*, page 644, beginning with ". . . add 25 ml. of diluted hydrochloric acid . . . ." The weight of barium sulfate so obtained, multiplied by 1.033, represents the weight of $C_7H_4NNaO_3S.2H_2O$ in the Tablets taken.

Packaging and storage—Preserve Sodium Cyclamate and Sodium Saccharin Tablets in tight containers.

Tablets available—Sodium Cyclamate and Sodium Saccharin Tablets usually available contain 50 mg. of sodium cyclamate and 5 mg. of sodium saccharin.

CATEGORY—See Sodium Cyclamate.

Sodium Dehydrocholate Injection

Sodium Dehydrocholate Injection is a sterile solution of $C_{24}H_{33}NaO_5$ (sodium dehydrocholate) in water for injection, usually prepared by neutralizing dehydrocholic acid for parenteral use. It contains not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_{24}H_{33}NaO_5$.

Identification—Transfer a portion of Sodium Dehydrocholate Injection, equivalent to about 100 mg. of sodium dehydrocholate, into a separator, add 10 ml. of water and acidify with diluted hydrochloric acid. Extract with three 15-ml. portions of chloroform, evaporate the combined chloroform extracts to dryness on a steam bath, and dry at 105° for 1 hour: the resulting dehydrocholic acid melts within a range of 3° between 231° and 242°, page 814.

pH, page 824—The pH of Sodium Dehydrocholate Injection is between 8.5 and 9.5.

Heavy metals, page 806—Dilute a volume of Sodium Dehydrocholate Injection, equivalent to 500 mg. of sodium dehydrocholate, to 25 ml. with water and add 5 drops of sodium sulfide T.S.: if a dark color is produced, it is not darker than that produced in a control to which 1 ml. of the standard lead solution has been added, corresponding to a heavy metals limit of 20 parts per million.

Pyrogen—Sodium Dehydrocholate Injection, diluted if necessary with water for injection to a concentration of 5 percent, meets the requirements of the *Pyrogen Test*, page 851, when administered in that concentration in doses of 3 ml./kg.

Other requirements—Sodium Dehydrocholate Injection meets the requirements under *Injections*, page 810.

Assay—Transfer an accurately measured quantity of Sodium Dehydrocholate Injection, equivalent to about 500 mg. of sodium dehydrocholate, to a continuous extraction apparatus for liquids heavier than water. Add 20 ml. of water and sufficient hydrochloric acid to neutralize the sample, and then add 2 ml. of hydrochloric acid in excess. Extract for 4 hours with chloroform. Cool the contents of the extraction apparatus and separate the chloroform, adding a few additional ml. of chloroform, if necessary, to ensure complete removal of the dehydrocholic acid. Evaporate the chloroform, and dissolve the residue in 40 ml. of neutralized alcohol. Add thymol blue T.S., and titrate with 0.1 *N* sodium hydroxide, adding 100 ml. of water just prior to the end-point. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 42.45 mg. of $C_{24}H_{33}NaO_5$.

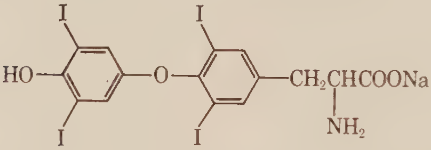
Packaging and storage—Preserve Sodium Dehydrocholate Injection in single-dose, light-resistant containers, preferably of Type I glass.

Injections available—Sodium Dehydrocholate Injection usually available contains the following amounts of sodium dehydrocholate: 500 mg. in 10 ml.; 600 mg. in 3 ml.; 1 g. in 5 ml.; and 2 g. in 10 ml.

CATEGORY—Choleretic; diagnostic aid (circulation time).

USUAL DOSE OF SODIUM DEHYDROCHOLATE—Intravenous, 3 to 5 ml. of a 20 percent solution.

Sodium Dextrothyroxine*



Sodium D-3-[4-(4-Hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]alanine

$C_{15}H_{10}I_4NNaO_4 . xH_2O$ Mol. wt. (anhydrous) 798.86

Sodium Dextrothyroxine contains not less than 97.0 percent and not more than 103.0 percent of $C_{15}H_{10}I_4NNaO_4$, calculated on the dried basis.

Description—Sodium Dextrothyroxine occurs as a light yellow to buff-colored, odorless, tasteless powder. It is stable in dry air but may assume a slight pink color upon exposure to light. The pH of a saturated solution is about 8.9.

Solubility—Sodium Dextrothyroxine is very slightly soluble in water. It is slightly soluble in alcohol, and is insoluble in acetone, in chloroform, and in ether. It is soluble in solutions of alkali hydroxides and in hot solutions of alkali carbonates.

Identification—

A: Ignite about 50 mg. of Sodium Dextrothyroxine in a platinum dish over a free flame: it decomposes and liberates iodine vapors.

B: Dissolve about 5 mg. of Sodium Dextrothyroxine in a mixture of 1 drop of hydrochloric acid and 2 ml. of 50 percent alcohol, add 1 drop of a 1 in 10 sodium nitrite solution, and boil: a yellow color is produced. Cool, and make the solution alkaline by the addition of ammonia T.S.: the solution color changes from yellow to red.

Specific rotation, page 822—The specific rotation of Sodium Dextrothyroxine, determined in a mixture of 1 part of 1 *N* sodium hydroxide and 2 parts of alcohol, containing the equivalent of 300 mg. of anhydrous sodium dextrothyroxine in each 10 ml., calculated on the dried basis, is between +5° and +6°.

Loss on drying, page 814—Dry Sodium Dextrothyroxine over phosphorus pentoxide at 60° and at a pressure not exceeding 10 mm. of mercury for 4 hours: it loses not more than 11 percent of its weight.

Soluble halides—Shake 10 mg. of Sodium Dextrothyroxine with 10 ml. of water containing 1 drop of diluted nitric acid for 5 minutes, filter, dilute the filtrate to 10 ml. with water, and add 3 drops of silver nitrate T.S.: any turbidity produced is not greater than that of a control containing 0.1 ml. of 0.02 *N* hydrochloric acid (0.71 percent as chloride).

Assay—Weigh accurately about 25 mg. of Sodium Dextrothyroxine, and proceed as directed under *Oxygen Flask Combustion,* page 823, using 10 ml. of 0.02 *N* sodium hydroxide as the absorbing liquid. After combustion is complete, allow the flask to cool, shake vigorously to complete the absorption, and allow the vapors to settle. Place a few ml. of water in the cup top, carefully withdraw the stopper, and rinse the stopper, platinum wire, platinum gauze, and sides of the flask with about

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* Patented. See notice, page ii.

20 ml. of water, added in small portions. Add 5 to 10 ml. of a solution prepared by adding 10 g. of potassium acetate and 0.4 ml. of bromine in sufficient glacial acetic acid to make 100 ml. Allow to stand for 2 minutes, then add 1 ml. of 90 percent formic acid, and rinse the sides of the flask with small portions of water. Add 1 g. of potassium iodide, and titrate with 0.1 *N* sodium thiosulfate, adding starch T.S. as the end-point is approached. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 3.329 mg. of $C_{15}H_{10}I_4NNaO_4$.

Packaging and storage—Preserve Sodium Dextrothyroxine in tight containers.

Category—Antihypercholesterolemic.

Usual dose—Initial, **1.0** to **2.0 mg.** daily; maintenance, **4.0** to **8.0 mg.** daily.

Usual dose range—**1.0** to **8.0 mg.** daily.

Sodium Dextrothyroxine Tablets

Sodium Dextrothyroxine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{10}I_4NNaO_4$.

Identification—To an amount of finely powdered Sodium Dextrothyroxine Tablets, equivalent to about 500 mcg. of sodium dextrothyroxine, add a mixture of 3 ml. of 50 percent alcohol and 0.2 ml. of hydrochloric acid, and boil gently for 30 seconds. Cool, add 0.1 ml. of a 1 in 10 sodium nitrite solution, and boil: a yellow color is produced. Cool, and make the solution alkaline by the addition of ammonia T.S.: the solution color changes from yellow to orange.

Disintegration, page 878—The disintegration time limit for Sodium Dextrothyroxine Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Sodium Dextrothyroxine Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Sodium Dextrothyroxine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 3 mg. of sodium dextrothyroxine, to a large nickel crucible, add an amount of anhydrous potassium carbonate equivalent to twice the weight of the powder taken (but in no case less than 8 g.), mix, and compact the mixture by gently tapping the crucible. Overlay the mixture with an additional 10 g. of anhydrous potassium carbonate, compact the charge by tapping the crucible, and ignite in a muffle furnace at 675° to 700° for 25 minutes. Cool the crucibel, add 20 ml. of water, heat gently to boiling, and decant the hot solution through a filter into a 500-ml. conical flask. Repeat the extraction with an additional 20 ml. of water, passing the hot solution through the same filter, and wash the crucible and filter with hot water until the filtrate in the flask measures about 200 ml. Cautiously add 40 ml. of dilute phosphoric acid (1 in 2), followed by 7 ml. of freshly prepared bromine T.S., and then boil until starch-iodide paper no longer is colored blue by the vapors. During the boiling, add water as necessary to maintain a volume of at least 200 ml. Rinse the walls of the flask with water, continue boiling for 5 minutes, cool, add 5 ml. of phenol solution (1 in 20), again rinse the walls of the flask with water, and allow to stand for 5 minutes. Add 2 ml. of dilute phosphoric acid (1 in 2) and 5 ml. of potassium iodide T.S., and titrate immediately with 0.01 *N* sodium thiosulfate from a 10-ml. microburet, adding starch T.S. as the end-point is neared. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* sodium thiosulfate is equivalent to 332.9 mcg. of $C_{15}H_{10}I_4NNaO_4$.

Packaging and storage—Preserve Sodium Dextrothyroxine Tablets in well-closed containers.

Tablets available—Sodium Dextrothyroxine Tablets usually available contain the following amounts of sodium dextrothyroxine: 2 and 4 mg.

Category and Dose—See Sodium Dextrothyroxine.

Sodium Hypochlorite Solution

Sodium Hypochlorite Solution contains not less than 4.0 percent and not more than 6.0 percent, by weight, of NaClO (sodium hypochlorite).

Caution: This Solution is not suitable for application to wounds.

Description—Sodium Hypochlorite Solution is a clear, pale greenish yellow liquid, having an odor of chlorine. It is affected by light.

Identification—

A: Sodium Hypochlorite Solution at first colors red litmus blue and then bleaches it.

B: The addition of diluted hydrochloric acid to Sodium Hypochlorite Solution causes an evolution of chlorine.

C: The solution obtained in *Identification test B* responds to the flame test for *Sodium*, page 810.

Assay—Weigh accurately, in a glass-stoppered flask, about 3 ml. of Sodium Hypochlorite Solution, and dilute it with 50 ml. of water. Add 2 g. of potassium iodide and 10 ml. of acetic acid, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 3.722 mg. of NaClO.

Packaging and storage—Preserve Sodium Hypochlorite Solution in tight, light-resistant containers, preferably at a temperature not above 25°.

NOTE: If *"Labarraque's Solution"* is ordered, Sodium Hypochlorite Solution, diluted with an equal volume of purified water, is to be dispensed.

CATEGORY—Disinfectant (see *Caution statement*).

Diluted Sodium Hypochlorite Solution

Diluted Sodium Hypochlorite Solution is a solution of chlorine compounds of sodium containing, in each 100 ml., not less than 450.0 mg. and not more than 500.0 mg. of NaClO.

Diluted Sodium Hypochlorite Solution may be prepared as follows:

Sodium Hypochlorite Solution	**1000 ml.**
Sodium Bicarbonate,	
Purified Water, of each, a sufficient quantity.	

Dilute the sodium hypochlorite solution with 5000 ml. of purified water and add 40 ml. of a 5 percent solution of sodium bicarbonate in cold purified water, and mix well. Remove about 20 ml. of the mixture, add to it about 20 mg. of powdered phenolphthalein, and shake it gently for 2 minutes. If a red color appears, add more of the sodium bicarbonate solution, and test with powdered phenolphthalein as just described, repeating the procedure as often as necessary until no red color is produced. Assay the liquid and dilute it with sufficient purified water to make the final solution contain, in each 100 ml., 480 mg. of NaClO.

Description—Diluted Sodium Hypochlorite Solution is a colorless or light yellow liquid having a slight odor suggesting chlorine.

Specific gravity, page 866—The specific gravity of Diluted Sodium Hypochlorite Solution is not more than 1.025.

Reaction—Add about 20 mg. of powdered phenolphthalein to 20 ml. of Diluted Sodium Hypochlorite Solution: no red color is produced in the mixture when agitated.

Residue on ignition—Add 5 drops of sulfuric acid to 10 ml. of Diluted Sodium Hypochlorite Solution, evaporate to dryness on a steam bath, and ignite the residue gently to constant weight: the weight of the residue does not exceed 300 mg. (3 percent).

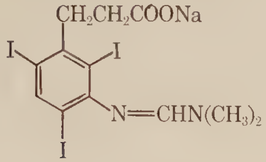
Assay—Pipet 15.0 ml. of Diluted Sodium Hypochlorite Solution into a conical flask, and dilute it with 25 ml. of water. Add 2 g. of potassium iodide and 10 ml. of acetic acid, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 3.722 mg. of NaClO.

Packaging and storage—Preserve Diluted Sodium Hypochlorite Solution in tight, light-resistant containers, and avoid excessive heat.

CATEGORY—Local anti-infective.

APPLICATION—Topically, full strength or diluted with 1 to 3 volumes of water.

Sodium Ipodate*



Sodium 3-[[(Dimethylamino)methylene]amino]-2,4,6-triiodohydrocinnamate

$C_{12}H_{12}I_3N_2NaO_2$ Mol. wt. 619.94

Sodium Ipodate contains not less than 97.5 percent and not more than 102.5 percent of $C_{12}H_{12}I_3N_2NaO_2$, calculated on the dried basis.

Description—Sodium Ipodate occurs as a white to off-white, odorless, fine crystalline powder.

Solubility—Sodium Ipodate is freely soluble in water, in alcohol, and in methanol, and is very slightly soluble in chloroform.

Identification—

A: Heat about 500 mg. of Sodium Ipodate in a porcelain crucible over a free flame: violet vapors of iodine are evolved.

B: Sodium Ipodate responds to the flame test for *Sodium*, page 810.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Sodium Ipodate, previously dried in vacuum at 60° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Sodium Ipodate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Sodium Ipodate in methanol exhibits maxima and minima at the same wavelengths as that of NF Sodium Ipodate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 235 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Sodium Ipodate in vacuum at 60° for 3 hours: it loses not more than 0.5 percent of its weight.

Iodide or iodine—Dissolve about 200 mg. of Sodium Ipodate in 10 ml. of acetic acid, add 2 ml. of 1 *N* sulfuric acid and 15 ml. of chloroform, and shake vigorously. Allow the layers to separate: the chloroform layer shows no more than a faint violet color. Add 1 ml. of 0.1 *N* potassium iodate, shake vigorously, and allow the layers to separate: the chloroform layer shows at most a slight trace of violet color.

Heavy metals, *Method II*, page 806—The heavy metals limit for Sodium Ipodate is 30 parts per million.

Assay—Transfer about 300 mg. of Sodium Ipodate, accurately weighed, to a 250-ml. glass-stoppered flask, add 30 ml. of sodium hydroxide solution (1 in 20) and 500 mg. of powdered zinc, and reflux the mixture for 60 minutes. Cool, wash the condenser with 20 ml. of water, and filter the mixture. Wash the flask and filter with small portions of water, adding the washings to the filtrate. Add to the filtrate 5 ml. of glacial acetic acid and 3 ml. of a mixture of 2 drops of nitric acid in 5 ml. of water, then add 3 drops of eosin Y T.S., and titrate with 0.05 *N* silver nitrate until the entire mixture changes to a permanent pink color. Each ml. of 0.05 *N* silver nitrate is equivalent to 10.33 mg. of $C_{12}H_{12}I_3N_2NaO_2$.

Packaging and storage—Preserve Sodium Ipodate in tight containers.

Category—Diagnostic aid (radiopaque-cholecystographic).

Usual dose—**3 g.** given 12 hours before the examination.

Usual dose range—**3 to 6 g.**

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* Patented. See notice, page ii.

Sodium Ipodate Capsules

Sodium Ipodate Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{12}H_{12}I_3N_2NaO_2$.

Identification—Transfer a portion of the contents of Sodium Ipodate Capsules, equivalent to about 2 g. of sodium ipodate, to a 250-ml. separator, add 100 ml. of water and 50 ml. of solvent hexane, and shake. Transfer the aqueous layer to a beaker, add 5 ml. of diluted hydrochloric acid, and mix. Filter, retain the filtrate, and wash the precipitate with several portions of water. Dry the precipitate in vacuum at 60° for 4 hours: the residue of 3-(dimethylaminomethyleneamino)-2,4,6-triiodohydrocinnamic acid responds to *Identification test A* under *Sodium Ipodate,* page 649, and a 1 in 100,000 solution of the residue in alcohol exhibits an ultraviolet absorbance maximum at 241 ± 2 mμ. The filtrate responds to the flame test for *Sodium,* page 810.

Weight variation, page 901—Sodium Ipodate Capsules meet the requirements of the weight variation test for capsules.

Assay—Place a number of Sodium Ipodate Capsules, equivalent to about 5 g. of sodium ipodate, in a 400-ml. beaker, add 200 ml. of sodium hydroxide T.S. and 50 ml. of solvent hexane, and stir mechanically until the capsules have completely disintegrated. Transfer the mixture to a 500-ml. separator, wash the beaker with a total of 25 ml. of sodium hydroxide T.S. in divided portions, and add the washings to the separator. Allow the layers to separate, and transfer the aqueous layer to a 500-ml. volumetric flask. Wash the solvent hexane layer with two 50-ml. portions of sodium hydroxide T.S., add the washings to the volumetric flask, dilute to volume with sodium hydroxide T.S., and mix well. Pipet 25.0 ml. of the solution, which may be milky in appearance, into a glass-stoppered 250-ml. conical flask, add 500 mg. of powdered zinc, and continue as directed in the *Assay* under *Sodium Ipodate,* page 649, beginning with "... and reflux the mixture for 60 minutes.

Packaging and storage—Preserve Sodium Ipodate Capsules in tight containers.

Capsules available—Sodium Ipodate Capsules usually available contain the following amount of sodium ipodate: 500 mg.

CATEGORY and DOSE—See Sodium Ipodate.

Sodium Methiodal

ICH$_2$SO$_3$Na

Sodium Iodomethanesulfonate

CH$_2$INaO$_3$S Mol. wt. 243.98

Sodium Methiodal, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 102.0 percent of CH$_2$INaO$_3$S.

Description—Sodium Methiodal occurs as a white, crystalline powder. It is odorless and has a slight saline taste, followed by a sweetish after-taste. On exposure to light it decomposes and becomes yellow. Its solutions are neutral to litmus.

Solubility—Sodium Methiodal is very soluble in water and in methanol. It is slightly soluble in alcohol, and practically insoluble in acetone, in ether, and in benzene.

Identification—

A: Fuse about 500 mg. of Sodium Methiodal with about 5 g. of powdered anhydrous sodium carbonate in a nickel crucible until decomposed. Allow to cool, dissolve the residue in 20 ml. of water, and filter through paper. Portions of the solution respond to the tests for *Iodide,* page 808.

B: To a portion of the solution prepared for *Identification test A* add 3 drops of freshly prepared sodium nitroferricyanide T.S.: a deep violet color is produced.

C: The residue from the ignition of Sodium Methiodal imparts an intense yellow color to a nonluminous flame.

Loss on drying, page 814—Dry Sodium Methiodal at 105° for 4 hours: it loses not more than 1 percent of its weight.

Halides—Dissolve about 200 mg. of Sodium Methiodal in 5 ml. of water, and add 1 ml. of diluted nitric acid and 1 ml. of silver nitrate T.S.: any turbidity produced corresponds to not more than 0.1 ml. of 0.02 *N* hydrochloric acid (0.035 percent).

Selenium—A *Test Preparation* prepared with 200 mg. of Sodium Methiodal meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Sulfate—To 5 ml. of a solution of Sodium Methiodal (1 in 25) add 1 ml. of diluted hydrochloric acid and 1 ml. of barium chloride T.S.: no turbidity is produced.

Arsenic—A *Test Preparation* prepared with 1.25 g. of Sodium Methiodal, as directed for organic compounds, meets the requirements of the *Arsenic Test,* page 777 (8 parts per million As).

Heavy metals—Dissolve 500 mg. of Sodium Methiodal in a mixture of 5 ml. of sodium hydroxide T.S. and 20 ml. of water, and add 5 drops of sodium sulfide T.S. Any darkening produced does not exceed that of a control made with the same quantities of the same reagents and to which

0.5 ml. of standard lead solution (page 813) has been added, corresponding to a heavy metals limit of 10 parts per million.

Assay—Place about 400 mg. of Sodium Methiodal, previously dried at 105° for 4 hours and accurately weighed, in a glass-stoppered, 250-ml. conical flask, add 30 ml. of sodium hydroxide solution (1 in 20) and 500 mg. of powdered zinc, and reflux the mixture for 1 hour. Cool to room temperature, wash the condenser with 20 ml. of water, and filter the mixture. Wash the flask and the filter with small portions of water, adding the washings to the filtrate. Add to the filtrate 5 ml. of glacial acetic acid and 1 ml. of tetrabromophenolphthalein ethyl ester T.S., and titrate with 0.05 *N* silver nitrate until the color of the yellow precipitate just changes to green. Each ml. of 0.05 *N* silver nitrate is equivalent to 12.20 mg. of CH_2INaO_3S.

Packaging and storage—Preserve Sodium Methiodal in tight, light-resistant containers.

CATEGORY—Diagnostic aid (radiopaque urographic).

USUAL DOSE—Intravenous, **20 g.** in 50 ml.

USUAL DOSE RANGE—**10** to **30 g.**

Sodium Methiodal Injection

Sodium Methiodal Injection is a sterile solution of sodium methiodal in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of CH_2INaO_3S.

Identification—The residue obtained upon evaporation of Sodium Methiodal Injection responds to the *Identification tests* under *Sodium Methiodal*, page 650.

pH, page 824—The pH of Sodium Methiodal Injection is between 5.0 and 8.0.

Pyrogen—Sodium Methiodal Injection meets the requirements of the *Pyrogen Test*, page 851, the Injection being diluted to contain 130 mg. of sodium methiodal in each ml.

Other requirements—Sodium Methiodal Injection meets the requirements under *Injections*, page 810.

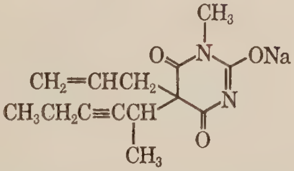
Assay—Pipet into a glass-stoppered, 250-ml. conical flask a volume of Sodium Methiodal Injection, equivalent to about 400 mg. of sodium methiodal. Proceed as directed in the *Assay* under *Sodium Methiodal*, page 650, beginning with "... add 30 ml. of sodium hydroxide solution ...."

Packaging and storage—Preserve Sodium Methiodal Injection in single-dose or in multiple-dose containers, preferably of Type I glass.

Injections available—Sodium Methiodal Injection usually available contains the following amounts of sodium methiodal: 10 and 20 g. in 50 ml.; 40 g. in 100 ml.

CATEGORY and DOSE—See Sodium Methiodal.

Sodium Methohexital for Injection*



Sodium 5-Allyl-1-methyl-5-(1-methyl-2-pentynyl)barbiturate

$C_{14}H_{17}N_2NaO_3$ Mol. wt. 284.29

Sodium Methohexital for Injection is a sterile mixture of sodium methohexital and anhydrous sodium carbonate as a buffer. It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{14}H_{17}N_2NaO_3$, calculated on the dried basis.

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* Patented. See notice, page ii.

Description—Sodium Methohexital for Injection occurs as a white to off-white hygroscopic powder. It is essentially odorless.

Completeness of solution—A 1-g. portion of Sodium Methohexital for Injection dissolves in 20 ml. of carbon dioxide-free water to yield a clear solution.

Identification—

A: Dissolve about 500 mg. of Sodium Methohexital for Injection in 10 ml. of water, and add an excess of diluted hydrochloric acid: a white precipitate of methohexital is formed.

B: Dissolve about 500 mg. of Sodium Methohexital for Injection in 10 ml. of water in a separator, add 10 ml. of diluted hydrochloric acid, and extract the liberated methohexital with two 25-ml. portions of chloroform. Evaporate the combined chloroform extracts to dryness, add 10 ml. of ether, evaporate again, and dry the residue in vacuum at 80° for 4 hours: the methohexital so obtained melts between 92° and 96°, page 814.

C: Dissolve 50 mg. of the residue obtained in *Identification test B* in 5 ml. of chloroform: the solution exhibits infrared absorption maxima at the same wavelengths as that of a similar preparation of NF Methohexital Reference Standard.

Other requirements—Sodium Methohexital for Injection meets the requirements under *Injections*, page 810.

Loss on drying, page 814—Dry Sodium Methohexital for Injection at 105° for 4 hours: it loses not more than 2 percent of its weight.

Heavy metals, *Method II*, page 806—The heavy metals limit for Sodium Methohexital for Injection is 10 parts per million.

pH, page 824—The pH of a solution of Sodium Methohexital for Injection (1 in 20) is between 10.6 and 11.6.

Weight variation, page 901—Sodium Methohexital for Injection meets the requirements of the weight variation test for sterile solids.

Assay—

Standard preparation—Transfer about 23 mg. of NF Methohexital Reference Standard, accurately weighed, to a 250-ml. volumetric flask, and add 50 ml. of water, 0.5 ml. of sodium hydroxide solution (1 in 10), and 1.5 mg. of anhydrous sodium carbonate. Mix, dilute to volume with water, and mix. Dilute 20.0 ml. of this solution to 100.0 ml. with water, and mix.

Assay preparation—Transfer about 110 mg. of Sodium Methohexital for Injection, accurately weighed, to a 1000-ml. volumetric flask. Add about 200 ml. of water, and 2.0 ml. of sodium hydroxide solution (1 in 10), mix, dilute to volume with water, and mix. Dilute 20.0 ml. of this solution to 100.0 ml. with water, and mix.

Procedure—Concomitantly determine the absorbance of the *Standard preparation* (A_S) and of the *Assay preparation* (A_U) in 1-cm. cells, at the maximum at about 247 mμ, with a suitable spectrophotometer, using freshly prepared sodium hydroxide solution (1 in 25,000) as the blank. Calculate the quantity, in mg., of $C_{14}H_{17}N_2NaO_3$ in the sample taken by the formula $5C \times 1.084 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and 1.084 is the ratio of the molecular weight of sodium methohexital to that of methohexital.

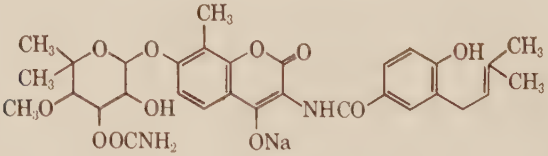
Packaging and storage—Preserve Sodium Methohexital for Injection in *Containers for Sterile Solids* as described under *Injections*, page 810.

Sizes available—Sodium Methohexital for Injection usually available contains the following amounts of sodium methohexital: 500 mg., 2.5 g., and 5.0 g.

CATEGORY—General anesthetic.

USUAL DOSE—Intravenous—Induction, **7.5 ml.** of 1 percent solution, at the rate of 1 ml. every 5 seconds. Maintenance, **2** to **4 ml.** every 4 to 6 minutes.

Sodium Novobiocin



$C_{31}H_{35}N_2NaO_{11}$ Novobiocin Monosodium Salt Mol. wt. 634.62

Sodium Novobiocin contains the equivalent of not less than 80.0 percent of novobiocin (as the free acid, $C_{31}H_{36}N_2O_{11}$), calculated on the dried basis. Sodium Novobiocin conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Sodium Novobiocin is a white or practically white, crystalline powder. It is odorless or practically odorless. It is hygroscopic.

Solubility—Sodium Novobiocin is very soluble in water, and is freely soluble in alcohol, in glycerin, and in propylene glycol.

Packaging and storage—Preserve Sodium Novobiocin in tight containers.

CATEGORY—Antibacterial.

USUAL DOSE—Oral, the equivalent of **250 mg.** of novobiocin every 6 hours. Intravenous and intramuscular, **500 mg.** every 12 hours.

USUAL DOSE RANGE—**1** to **2 g.** daily in 4 divided doses.

Sodium Novobiocin Capsules

Sodium Novobiocin Capsules contain an amount of sodium novobiocin equivalent to not less than 90.0 percent and not more than 120.0 percent of the labeled amount of novobiocin (as the free acid, $C_{31}H_{36}N_2O_{11}$). Sodium Novobiocin Capsules conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Sodium Novobiocin Capsules in well-closed containers.

Capsules available—Sodium Novobiocin Capsules usually available contain the equivalent of the following amount of novobiocin: 250 mg.

CATEGORY and DOSE—See Sodium Novobiocin.

Sodium Novobiocin for Injection

Sodium Novobiocin for Injection is sterile sodium novobiocin, and may contain suitable solubilizing agents, preservatives, and diluents. It contains not less than 90.0 percent and not more than 120.0 percent of the labeled amount of novobiocin (as the free acid, $C_{31}H_{36}N_2O_{11}$). Sodium Novobiocin for Injection conforms to the regulations of the federal Food and Drug Administration concerning the certification of antibiotic drugs.

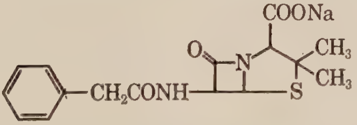
Packaging and storage—Preserve Sodium Novobiocin for Injection in single-dose or in multiple-dose containers.

Labeling—Sodium Novobiocin for Injection complies with the requirements for *Labeling* under *Injections*, page 810. The container label indicates the solvent recommended for preparing a solution for injection.

Size available—Sodium Novobiocin for Injection usually available contains the following amount of novobiocin: 500 mg.

CATEGORY and DOSE—See Sodium Novobiocin.

Sodium Penicillin G



Sodium Benzylpenicillin
Sodium 3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylate

$C_{16}H_{17}N_2NaO_4S$ Mol. wt. 356.38

Sodium Penicillin G contains not less than 85.0 percent of $C_{16}H_{17}N_2NaO_4S$, and not less than 90.0 percent of total penicillins, calculated as sodium penicillin G. Sodium Penicillin G conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Sodium Penicillin G occurs as colorless or white crystals, or as a white to slightly yellow, crystalline powder. It is odorless or practically so, and is moderately hygroscopic. Its solutions are dextrorotatory. It is relatively stable in air, but is inactivated by prolonged heating at about 100°, especially in the presence of moisture. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15°. Its solutions are rapidly inactivated by acids, alkali hydroxides, oxidizing agents, and penicillinase.

Packaging and storage—Preserve Sodium Penicillin G in tight containers. Preserve Sodium Penicillin G intended for parenteral use in *Containers for Sterile Solids* as described under *Injections*, page 810.

When the Sodium Penicillin G is packaged for dispensing, the container is of colorless, transparent glass, with a closure through which a hypodermic needle may be introduced and withdrawn without destroying its effectiveness. Each container holds 100,000, 200,000, 300,000, or 500,000 units (60, 120, 180, or 300 mg.), or 1,000,000 units (600 mg.) or whole multiples thereof up to and including 5,000,000 units, except that when packaged and labeled solely for intravenous infusion each such container may contain 20,000,000 units (12 g.), and except that when packaged and labeled solely for dental use each such container may contain not less than 10,000 units (6 mg.).

Labeling—The container label and the package label of Sodium Penicillin G bear the lot number or the identifying mark, the number of units or the weight of penicillin in the container, and the expiration date, which is from 1 year up to 5 years, depending upon the substantiating data submitted with the application for certification, from the end of the calendar month in which the lot was last assayed and released by the manufacturer. When Sodium Penicillin G complies only with the standards for oral or nonparenteral use, the label so indicates. The penicillin content may be declared on the label in mg., in g., or in penicillin units.

If the Sodium Penicillin G is packaged for dispensing, the statement, "Sterile solutions may be kept in a refrigerator for 3 days without significant loss of potency," appears in the labeling.

CATEGORY—Antibacterial.

USUAL DOSE—Oral and intramuscular, **400,000 units** four times a day; intravenous, **10,000,000 units** daily.

NOTE: One penicillin unit is the antibiotic activity of 0.6 mcg. of FDA Sodium Penicillin G Master Standard, 1 mg. of which represents 1667 units.

Sodium Penicillin G for Injection

Sodium Penicillin G for Injection is a sterile, dry mixture of sodium penicillin G and suitable buffers. It contains not less than 90.0 percent of the labeled amount of sodium penicillin G. Sodium Penicillin G for Injection conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Sodium Penicillin G for Injection in single-dose or multiple-dose containers.

Size available—Sodium Penicillin G for Injection usually available contains the following amount of sodium penicillin G: 5,000,000 units.

CATEGORY and DOSE—See Sodium Penicillin G.

Sodium Phosphate

Disodium Hydrogen Phosphate

$Na_2HPO_4.7H_2O$ Mol. wt. 268.07

Sodium Phosphate, dried at 105° for 12 hours, contains not less than 98.0 percent and not more than 100.5 percent of Na_2HPO_4.

Description—Sodium Phosphate occurs as a colorless or white, granular salt. It effloresces in warm, dry air. Its solutions are alkaline to phenolphthalein T.S., a 0.1 *M* solution having a pH of about 9.5.

Solubility—Sodium Phosphate is freely soluble in water. It is very slightly soluble in alcohol.

Identification—A solution of Sodium Phosphate (1 in 20) responds to the tests for *Sodium*, page 810, and for *Phosphate*, page 809.

Loss on drying, page 814—Dry Sodium Phosphate at 105° for 12 hours: it loses not less than 43 percent and not more than 50 percent of its weight.

Insoluble substances—Dissolve 10 g. of Sodium Phosphate in 100 ml. of hot water, filter through a tared filtering crucible, wash the insoluble residue with hot water, and dry at 105° for 2 hours: the residue does not exceed 20 mg. (0.2 percent).

Chloride, page 784—One g. of Sodium Phosphate shows no more chloride than corresponds to 0.4 ml. of 0.02 *N* hydrochloric acid (0.028 percent).

Sulfate, page 784—A 200-mg. portion of Sodium Phosphate shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (0.1 percent).

Arsenic—A solution of 1.25 g. of Sodium Phosphate in water meets the requirements of the *Arsenic Test,* page 777 (8 parts per million As).

Heavy metals, page 806—Dissolve 2 g. of Sodium Phosphate in 10 ml. of water, add 4 ml. of diluted acetic acid, and sufficient water to make 25 ml.: the heavy metals limit for Sodium Phosphate is 10 parts per million.

Assay—Transfer about 6.5 g. of Sodium Phosphate, previously dried at 105° for 12 hours and accurately weighed, to a 250-ml. beaker, add 50.0 ml. of 1 *N* hydrochloric acid and 50 ml. of water, and stir until the sample is completely dissolved. Place the electrodes of a suitable pH meter in the solution, and titrate the excess acid with 1 *N* sodium hydroxide to the inflection point occurring at about pH 4. Record the buret reading, and calculate the volume (*A*) of 1 *N* hydrochloric acid consumed by the sample. Continue the titration with 1 *N* sodium hydroxide until the inflection point occurring at about pH 8.8 is reached, record the buret reading, and calculate the volume (*B*) of 1 *N* sodium hydroxide required in the titration between the two inflection points (pH 4 to pH 8.8). When *A* is equal to, or less than, *B*, each ml. of the volume *A* of 1 *N* hydrochloric acid is equivalent to 142.0 mg. of Na_2HPO_4. When *A* is greater than *B*, each ml. of the volume $2B - A$ of 1 *N* sodium hydroxide is equivalent to 142.0 mg. of Na_2HPO_4.

Packaging and storage—Preserve Sodium Phosphate in tight containers.

CATEGORY—Cathartic.
USUAL DOSE—**4 g.**
USUAL DOSE RANGE—**4 to 8 g.**

Dried Sodium Phosphate

$Na_2HPO_4 . xH_2O$ Mol. wt. (anhydrous) 141.96

Dried Sodium Phosphate, dried at 105° for 4 hours, contains not less than 98.0 percent and not more than 100.5 percent of Na_2HPO_4.

Description—Dried Sodium Phosphate occurs as a white powder which readily absorbs moisture.

Solubility—Dried Sodium Phosphate is freely soluble in water. It is insoluble in alcohol.

Identification—A solution of Dried Sodium Phosphate (1 in 30) responds to the tests for *Sodium*, page 810, and for *Phosphate*, page 809.

Loss on drying, page 814—Dry Dried Sodium Phosphate at 105° for 4 hours: it loses not more than 5 percent of its weight.

Other tests—Proper allowance being made for the absence of water of hydration, Dried Sodium Phosphate meets the requirements of the tests for *Insoluble substances, Chloride, Sulfate, Arsenic,* and *Heavy metals,* under *Sodium Phosphate,* page 654.

Assay—Transfer about 3 g. of Dried Sodium Phosphate, previously dried at 105° for 4 hours and accurately weighed, to a 250-ml. beaker, add 50.0 ml. of 1 *N* hydrochloric acid and 50 ml. of water, and stir until the sample is completely dissolved. Place the electrodes of a suitable pH meter in the solution, and titrate the excess acid with 1 *N* sodium hydroxide to the inflection point occurring at about pH 4. Record the buret reading, and calculate the volume (*A*) of 1 *N* hydrochloric acid consumed by the sample. Continue the titration with 1 *N* sodium hydroxide until the inflection point occurring at about pH 8.8 is reached, record the buret reading, and calculate the volume (*B*) of 1 *N* sodium hydroxide required in the titration between the two inflection points (pH 4 to pH 8.8). When *A* is equal to, or less than, *B*, each ml. of the volume *A* of 1 *N* hydrochloric acid is equivalent to 142.0 mg. of Na_2HPO_4. When *A* is greater than *B*, each ml. of the volume $2B - A$ of 1 *N* sodium hydroxide is equivalent to 142.0 mg. of Na_2HPO_4.

Packaging and storage—Preserve Dried Sodium Phosphate in tight containers.

CATEGORY—See Sodium Phosphate.
USUAL DOSE RANGE—**2 to 4 g.**

Effervescent Sodium Phosphate

Dried Sodium Phosphate, dried and powdered	**200 g.**
Sodium Bicarbonate, in dry powder	**477 g.**
Tartaric Acid, in dry powder	**252 g.**
Citric Acid, monohydrate	**162 g.**
To make about	**1000 g.**

Powder the citric acid, mix it intimately with the dried sodium phosphate and tartaric acid, and thoroughly incorporate the sodium bicarbonate.

Place the mixed powders on a plate of glass or in a suitable dish in an oven previously heated to between 93° and 104°. Manipulate the mixture carefully, with a spatula which is acid-resistant, and when it has become moist rub it through a No. 6 tinned-iron sieve. Dry the granules at a temperature not exceeding 54°, immediately transfer the salt to suitable containers, and seal them tightly.

NOTE: The proportions of tartaric acid and citric acid may be varied if desired, but their combined acidity must be equivalent to the acidity indicated in the official formula.

Packaging and storage—Preserve Effervescent Sodium Phosphate in tight containers.

CATEGORY—See Sodium Phosphate.
USUAL DOSE RANGE—**10** to **20 g.**

Sodium Phosphate Solution

Sodium Phosphate Solution contains, in each 100 ml., the equivalent of not less than 71.0 g. and not more than 79.0 g. of $Na_2HPO_4 \cdot 7H_2O$.

Sodium Phosphate	**755 g.**
Citric Acid, monohydrate	**130 g.**
Glycerin	**150 ml.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Add the sodium phosphate, the citric acid, and the glycerin to 150 ml. of purified water, and digest on a steam bath until solution is effected. Filter, and pass sufficient purified water through the filter to make the product measure 1000 ml.

NOTE: 400 g. of dried sodium phosphate may be used in place of the 755 g. of sodium phosphate specified in the formula. If this alternative is followed, the 150 ml. of purified water specified in the directions should be increased to 500 ml.

Description—Sodium Phosphate Solution is a clear, colorless liquid, of a thick, syrupy consistency, practically odorless, and with a cooling, salty taste. It is acid to litmus. Its specific gravity is about 1.39.

Identification—Sodium Phosphate Solution responds to the tests for *Sodium,* page 810, and for *Phosphate,* page 809.

Arsenic—A 1.25 g. portion of Sodium Phosphate Solution meets the requirements of *Arsenic Test,* page 777 (8 parts per million As).

Heavy metals, page 806—To 1.0 g. of Sodium Phosphate Solution add 1 ml. of diluted acetic acid and enough water to make 25 ml.: the heavy metals limit of Sodium Phosphate Solution is 10 parts per million.

Assay—Pipet 5.0 ml. of Sodium Phosphate Solution into a 100-ml. volumetric flask, and dilute to volume with water. Mix, and pipet 10.0 ml. of the diluted solution into a beaker. Dilute to 200 ml. with water, add 5 ml. of hydrochloric acid, an excess (15 ml.) of magnesia mixture T.S., and 40 ml. of ammonia T.S. Mix, and allow to stand overnight. Collect the precipitate in a tared, previously ignited and weighed filtering crucible, and wash it with a mixture of 1 volume of ammonia T.S. and 3 volumes of water until free from chloride. Add a few crystals of ammonium nitrate or a few drops of a saturated solution of ammonium nitrate to the crucible, and dry at 105°. Ignite the precipitate carefully, starting with a very low heat and gradually increasing to a bright redness until constant weight is obtained. The weight of the magnesium pyrophosphate so obtained, multiplied by 2.409, indicates its equivalent of $Na_2HPO_4 . 7H_2O$.

Packaging and storage—Preserve Sodium Phosphate Solution in tight containers, in a moderately warm place (not under 22°).

Category—See Sodium Phosphate.

Usual dose—**10 ml.**

One usual dose contains about 8 g. of Sodium Phosphate.

Sodium Potassium Tartrate, page 577

Sodium Propionate

CH_3CH_2COONa

$C_3H_5NaO_2 . xH_2O$ Mol. wt. (anhydrous) 96.06

Sodium Propionate, dried at 105° for 2 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_3H_5NaO_2$.

Description—Sodium Propionate occurs as colorless, transparent crystals or as a granular, crystalline powder. It is odorless, or has a faint acetic-butyric odor. It is deliquescent in moist air.

Solubility—Sodium Propionate is very soluble in water and is soluble in alcohol.

Identification—

A: A solution of Sodium Propionate (1 in 20) responds to the tests for *Sodium*, page 810.

B: Upon ignition, Sodium Propionate yields an alkaline residue which effervesces with acids.

C: Warm Sodium Propionate with sulfuric acid: propionic acid, recognizable by its odor, is evolved.

Loss on drying, page 814—Dry Sodium Propionate at 105° for 2 hours: it loses not more than 5 percent of its weight.

Alkalinity—Dissolve 2 g. of Sodium Propionate in 20 ml. of water, and add 3 drops of phenolphthalein T.S.: if a pink color is produced, it is discharged by 0.6 ml. of 0.1 *N* sulfuric acid.

Arsenic—A *Test Preparation* prepared with 1.25 g. of Sodium Propionate, as directed for organic compounds, meets the requirements of the *Arsenic Test*, page 777 (8 parts per million As).

Heavy metals, page 806—Dissolve 1 g. of Sodium Propionate in 1 ml. of 1 *N* acetic acid and sufficient water to make 25 ml.: the heavy metals limit for Sodium Propionate is 10 parts per million.

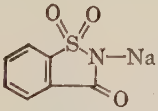
Assay—Dissolve about 200 mg. of Sodium Propionate, previously dried at 105° for 2 hours and accurately weighed, in 50 ml. of glacial acetic acid. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 9.606 mg. of $C_3H_5NaO_2$.

Packaging and storage—Preserve Sodium Propionate in tight containers.

Category—Local antifungal.

For external use—Topically in dosage forms containing 5 to 10 percent of Sodium Propionate.

Sodium Saccharin



$. 2\ H_2O$

1,2-Benzisothiazolin-3-one 1,1-Dioxide Sodium Salt

$C_7H_4NNaO_3S . 2H_2O$ Mol. wt. 241.20

Sodium Saccharin contains not less than 98.0 percent and not more than 101.0 percent of $C_7H_4NNaO_3S$, calculated on the anhydrous basis.

Description—Sodium Saccharin occurs as white crystals or as a white, crystalline powder. It is odorless or has a faint, aromatic odor, and has an intensely sweet taste even in dilute solutions. Sodium Saccharin in dilute solution is about 300 times as sweet as sucrose. When in powdered form it usually contains about one-third the theoretical amount of water of hydration as a result of efflorescence.

Solubility—Sodium Saccharin is freely soluble in water and is sparingly soluble in alcohol.

Identification—

A: Dissolve about 100 mg. of Sodium Saccharin in 5 ml. of sodium hydroxide solution (1 in 20), evaporate the solution to dryness, and gently fuse the residue over a small flame until it no longer evolves ammonia. Allow the residue to cool, dissolve it in 20 ml. of water, neutralize the solution with diluted hydrochloric acid, and filter: the addition of a drop of ferric chloride T.S. to the filtrate produces a violet color.

B: Mix 20 mg. of Sodium Saccharin with 40 mg. of resorcinol, add 10 drops of sulfuric acid, and heat the mixture in a suitable liquid bath at 200° for 3 minutes. Allow it to cool, and add 10 ml. of water and an excess of sodium hydroxide T.S.: a fluorescent green liquid results.

C: The residue obtained by igniting Sodium Saccharin responds to the tests for *Sodium*, page 810.

D: To 10 ml. of a solution of Sodium Saccharin (1 in 10) add 1 ml. of hydrochloric acid: a crystalline precipitate of saccharin is formed. Wash the precipitate well with cold water, and dry at 105° for 2 hours: it melts between 226° and 230°, page 814.

Alkalinity—A solution of Sodium Saccharin (1 in 10) is neutral or alkaline to litmus, but produces no red color with phenolphthalein T.S.

Water, page 900—Determine the water content of Sodium Saccharin by the titrimetric method: not less than 3 percent and not more than 15 percent is found.

Benzoate and salicylate—To 10 ml. of a solution of Sodium Saccharin (1 in 20) previously acidified with 5 drops of acetic acid, add 3 drops of ferric chloride T.S.: no precipitate or violet color appears.

Selenium—A *Test Preparation* prepared with 200 mg. of Sodium Saccharin meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Heavy metals, page 806—Dissolve 2 g. of Sodium Saccharin in 48 ml. of water, add 2 ml. of diluted acetic acid, mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, then filter through a dry filter, rejecting the first 10 ml. of filtrate: the heavy metals limit for Sodium Saccharin, determined on 25 ml. of the subsequent filtrate, is 20 parts per million.

Readily carbonizable substances, page 856—Dissolve 200 mg. of Sodium Saccharin in 5 ml. of sulfuric acid T.S., and keep at a temperature of 48° to 50° for 10 minutes: the solution has no more color than Matching Fluid A.

Assay—Accurately weigh about 500 mg. of Sodium Saccharin, and transfer completely to a separator with the aid of 10 ml. of water. Add 2 ml. of diluted hydrochloric acid, and extract the precipitated saccharin first with 30 ml., then with four 20-ml. portions, of a solvent composed of 9 volumes of chloroform and 1 volume of alcohol, filtering each extract through a small filter paper moistened with the solvent. Evaporate the combined filtrates on a steam bath, with the aid of a current of air, to dryness, then dissolve the residue in 75 ml. of hot water, cool, add phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 20.52 mg. of $C_7H_4NNaO_3S$.

Packaging and storage—Preserve Sodium Saccharin in well-closed containers.

CATEGORY—Non-nutritive sweetener.

Sodium Saccharin Tablets

Sodium Saccharin Tablets contain not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_7H_4NNaO_3S.2H_2O$.

Identification—Dissolve a quantity of Sodium Saccharin Tablets, equivalent to about 1 g. of sodium saccharin, in 10 ml. of water, filter if necessary, and to the solution add 5 ml. of diluted hydrochloric acid: a white precipitate of saccharin is formed. Collect the precipitate on a filter, wash it with small portions of cold water until the last washing is practically free from chloride, and dry it at 105° for 2 hours: the saccharin so obtained melts between 226° and 230°, page 814, and responds to the following tests:

A: Dissolve 100 mg. of the saccharin obtained under *Identification* in 5 ml. of sodium hydroxide solution (1 in 20), evaporate the solution to dryness, and gently fuse the residue until it no longer evolves ammonia, cool, dissolve in 20 ml. of water, neutralize with diluted hydrochloric acid, and filter: the addition of a drop of ferric chloride T.S. to the filtrate produces a violet color.

B: Mix 20 mg. of the saccharin obtained under *Identification* with 40 mg. of resorcinol, add 10 drops of sulfuric acid, heat in a suitable bath at 200° for 3 minutes, cool, and add 10 ml. of water and an excess of sodium hydroxide T.S.: a fluorescent green liquid results.

Ammonium salts—Dissolve a quantity of powdered Sodium Saccharin Tablets, equivalent to about 300 mg. of sodium saccharin in 5 ml. of water, and warm with 3 ml. of sodium hydroxide T.S.: the odor of ammonia is not perceptible.

Solution—Place 5 Sodium Saccharin Tablets in a 250-ml. beaker containing 150 ml. of water at 25°. Stir the solution for 5 minutes: all of the Tablets dissolve to give a clear or practically clear solution.

Content uniformity, *Method I,* page 799—Sodium Saccharin Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Sodium Saccharin Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 120 mg. of sodium saccharin, to a 100-ml. volumetric flask, add about 50 ml. of water, agitate until the tablet material is dissolved or evenly dispersed, dilute to volume with water, and mix. Transfer 10.0 ml. to a separator, add 2 ml. of diluted hydrochloric acid, and extract with five 20-ml. portions of a solvent composed of 9 volumes of chloroform and 1 volume of alcohol, filtering each extract through paper previously washed with the solvent. Collect the combined extracts in a beaker and evaporate on a steam bath, with the aid of a current of air, to dryness. Dissolve the residue in 10 ml. of 0.1 *N* sodium hydroxide and quantitatively transfer the solution with the aid of water to a 200-ml. volumetric flask, add water to volume, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Saccharin Reference Standard, in the same medium, at a concentration of about 50 mcg. per ml., in 1-cm. cells, at the maximum at about 269 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_7H_4NNaO_3S.2H_2O$ in the portion of Tablets taken by the formula $2C \times 1.317 \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., 1.317 is the conversion factor relating sodium saccharin to saccharin, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Sodium Saccharin Tablets in well-closed containers.

Tablets available—Sodium Saccharin Tablets usually available contain the following amounts of sodium saccharin: 15, 30, and 60 mg.

CATEGORY—See Sodium Saccharin.

Sodium Saccharin and Sodium Cyclamate Solution, page 644
Sodium Saccharin and Sodium Cyclamate Tablets, page 644

Sodium Secobarbital and Sodium Amobarbital Capsules

Sodium Secobarbital and Sodium Amobarbital Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_{12}H_{17}N_2NaO_3$ (sodium secobarbital) and of $C_{11}H_{17}N_2NaO_3$ (sodium amobarbital).

Identification—

A: Suspend the contents of one Sodium Secobarbital and Sodium Amobarbital Capsule in 10 ml. of water, and filter: the filtrate responds to the flame test for *Sodium,* page 810.

B: The chromatogram of the *Assay preparation,* prepared as directed in the *Assay,* conforms qualitatively with that of the *Standard preparation,* prepared as directed in the *Assay.*

Content uniformity, *Method I,* page 798—Sodium Secobarbital and Sodium Amobarbital Capsules meet the requirements of the content uniformity test for capsules, when assayed for both sodium secobarbital and sodium amobarbital.

Assay—

Internal standard solution—Dissolve 75.0 mg. of NF Aprobarbital Reference Standard, accurately weighed, in sufficient chloroform to make 100.0 ml.

Standard preparation—Dissolve 91.6 mg. of USP Secobarbital Reference Standard and 91.2 mg. of USP Amobarbital Reference Standard, accurately weighed, in sufficient chloroform to make 100.0 ml.

Assay preparation—Weigh the contents of not less than 20 Sodium Secobarbital and Sodium Amobarbital Capsules, and mix the contents thoroughly. Transfer an accurately weighed portion of the powder, equivalent to 100 mg. of sodium secobarbital, to a separator, add 20 ml. of water and 1 ml. of hydrochloric acid, and shake for 3 minutes with 100.0 ml. of chloroform. Remove the chloroform layer and use as directed in the *Procedure.*

Procedure—Mix 5.0 ml. of the *Standard* *preparation* with 5.0 ml. of the *Internal standard solution*, and inject an appropriate volume of this mixture into a suitable gas chromatograph equipped with a flame-ionization detector, and record the chromatogram. Under typical conditions the instrument contains a 1.2-meter × 6-mm. (outside diameter) glass U-tube packed with 3.8 percent silicone gum (General Electric SE-30, or W98, or equivalent) on 80 to 100-mesh silanized chromatographic siliceous earth. The column is maintained at 160°, and the injector port and the detector block at 285°; helium is used as the carrier gas at a flow rate of 55 ml. per minute; in the detector, maintain hydrogen at a flow rate of 35 ml. per minute, and oxygen at a flow rate of 300 ml. per minute.

Measure the heights of the first (aprobarbital), second (amobarbital), and third (secobarbital) peaks, and record the values as P_1, P_2, and P_3, respectively. Calculate the standard secobarbital ratio, R_S, and the standard amobarbital ratio, R_A, by the formulas $R_S = P_3/P_1$, and $R_A = P_2/P_1$.

Mix 5.0 ml. of the *Assay preparation* with 5.0 ml. of the *Internal standard solution*, inject an appropriate volume into the chromatograph, and record the chromatogram under the same conditions as described for the *Standard preparation*. Measure the heights of the first (aprobarbital), second (amobarbital), and third (secobarbital) peaks, and record the values as p_1, p_2, and p_3, respectively. Calculate the sample secobarbital ratio, r_S, and the sample amobarbital ratio, r_A, by the formulas $r_S = p_3/p_1$, and $r_A = p_2/p_1$, respectively.

Calculate the quantity, in mg., of $C_{12}H_{17}N_2NaO_3$ (sodium secobarbital) in the portion of the Capsules taken by the formula $1.092 \times (r_S/R_S) \times W$, in which 1.092 is the ratio of the molecular weight of sodium secobarbital to that of secobarbital, and W is the weight, in mg., of USP Secobarbital Reference Standard taken for the *Standard preparation*.

Calculate the quantity, in mg., of $C_{11}H_{17}N_2NaO_3$ (sodium amobarbital) in the portion of Capsules taken by the formula $1.097 \times (r_A/R_A) \times w$, in which 1.097 is the ratio of the molecular weight of sodium amobarbital to that of amobarbital, and w is the weight, in mg., of USP Amobarbital Reference Standard taken for the *Standard preparation*.

Packaging and storage—Preserve Sodium Secobarbital and Sodium Amobarbital Capsules in well-closed containers.

Capsules available—Sodium Secobarbital and Sodium Amobarbital Capsules usually available contain the following amounts of sodium secobarbital and sodium amobarbital: 25, 50, and 100 mg. of each.

CATEGORY—Sedative.

USUAL HYPNOTIC DOSE RANGE OF SODIUM SECOBARBITAL—**50** to **200 mg.** at bedtime; OF SODIUM AMOBARBITAL—**50** to **200 mg.** at bedtime.

Sodium Stearate

Sodium Stearate consists chiefly of $C_{18}H_{35}NaO_2$ (sodium stearate) and $C_{16}H_{31}NaO_2$ (sodium palmitate).

Description—Sodium Stearate is a fine, white powder, soapy to the touch. It usually has a slight, tallow-like odor. It is affected by light. Its solutions are alkaline to phenolphthalein T.S.

Solubility—Sodium Stearate is slowly soluble in cold water and in cold alcohol, but is readily soluble in hot water and in hot alcohol.

Identification—

A: When heated, Sodium Stearate fuses. At a high temperature it decomposes, emitting flammable vapors and the odor of burning fat, finally leaving a residue which, when moistened with water, is alkaline to litmus paper, effervesces with acids, and colors a nonluminous flame intensely yellow.

B: Dissolve 25 g. of Sodium Stearate in 300 ml. of hot water, add 60 ml. of diluted sulfuric acid, and heat the solution, with frequent stirring, until the separated fatty acid layer is clear. Wash the fatty acids with boiling water until free from sulfate, collect them in a small beaker, and warm on a steam bath until the water has settled and the fatty acids are clear. Allow the acids to cool, pour off the water layer, then melt the acids, filter into a dry beaker while hot, and dry at 105° for 20 minutes: the solidification temperature of the fatty acids is not below 54°, page 794.

Acidity or alkalinity—Weigh accurately 2 g. of Sodium Stearate, dissolve it in 50 ml. of neutralized alcohol with the aid of a little heat, and add 3 drops of phenolphthalein T.S.: no pink color is produced. Titrate the solution with 0.1 *N* sodium hydroxide until a pink color is produced: not less than 0.60 ml. and not more than 0.85 ml. of 0.1 *N* sodium hydroxide is required (0.85 to 1.2 percent as stearic acid).

Loss on drying, page 814—Tare a beaker containing about 1 g. of washed sand, previously dried at 105°, add about 500 mg. of Sodium Stearate, and reweigh. Add 10 ml. of alcohol, evaporate the mixture at about 80° to dryness, and dry at

105° for 4 hours: it loses not more than 5 percent of its weight.

Alcohol-insoluble substances—Reflux 1 g. of Sodium Stearate with 25 ml. of alcohol: it dissolves completely and the resulting solution is clear or not more than slightly opalescent.

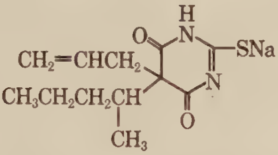
Iodine value of fatty acids, page 804—The iodine value of the fatty acids obtained in *Identification test B* is not more than 4.

Acid value of fatty acids, page 804—The acid value as determined on 1 g. of the fatty acids obtained in *Identification test B* is not less than 196 and not more than 211.

Packaging and storage—Preserve Sodium Stearate in well-closed, light-resistant containers.

CATEGORY—Emulsifying and stiffening agent.

Sodium Thiamylal for Injection



Sodium 5-Allyl-5-(1-methylbutyl)-2-thiobarbiturate

$C_{12}H_{17}N_2NaO_2S$ Mol. wt. 276.34

Sodium Thiamylal for Injection is a sterile mixture of sodium thiamylal with anhydrous sodium carbonate as a buffer. It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{12}H_{17}N_2NaO_2S$, calculated on the dried basis.

Description—Sodium Thiamylal for Injection occurs as a pale yellow, hygroscopic powder, having a disagreeable odor.

Completeness of solution, page 794—A 500-mg. portion of Sodium Thiamylal for Injection dissolves in 10 ml. of carbon dioxide-free water to yield a clear solution.

Identification—

A: Dissolve about 500 mg. of Sodium Thiamylal for Injection in 10 ml. of water, and add an excess of diluted hydrochloric acid: a white precipitate of thiamylal is formed.

B: Ignite about 500 mg. of Sodium Thiamylal for Injection: the residue responds to the tests for *Carbonate,* page 808, and for *Sodium,* page 810.

C: The residue of thiamylal obtained in the *Assay* melts between 133° and 139°, page 814.

Sterility—Sodium Thiamylal for Injection meets the requirements under *Sterility Tests,* page 874.

pH, page 824—The pH of a solution of Sodium Thiamylal for Injection (1 in 40) is between 10.5 and 11.0.

Loss on drying, page 814—Dry Sodium Thiamylal for Injection at 105° for 1 hour: it loses not more than 2 percent of its weight.

Selenium—A *Test Preparation* prepared with 200 mg. of Sodium Thiamylal for Injection meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Heavy metals, *Method II,* page 806—The heavy metals limit for Sodium Thiamylal for Injection is 30 parts per million.

Free thiamylal—Place about 1 g. of Sodium Thiamylal for Injection, accurately weighed, in a glass-stoppered cylinder, add 50 ml. of benzene, stopper, and shake the mixture for 10 minutes. Decant the supernatant liquid through filter paper into a tared beaker, and extract twice more, using 25 ml. and 15 ml. of benzene, respectively, and the same filter. Evaporate the combined filtrates to dryness, and dry the residue at 105° for 30 minutes: the weight of the residue is not more than 0.5 percent of the weight of the Sodium Thiamylal for Injection taken.

Weight variation, page 901—Sodium Thiamylal for Injection meets the requirements of the weight variation test for sterile solids.

Assay—Dissolve the contents of 10 containers of Sodium Thiamylal for Injection in sufficient water, and dilute quantitatively to obtain a solution containing about 50 mg. of sodium thiamylal in each ml. Transfer 10.0 ml. of the solution to a separator, add 40 ml. of water and 5 ml. of diluted hydrochloric acid, and proceed as directed under *Barbiturate Assay,* page 781, beginning with "Completely extract the liberated . . . ," using five 25-ml. portions of chloroform. Omit the addition of 10 ml. of ether and re-evaporation. Dry the residue at 105° for 30 minutes. The weight of the dried thiamylal, multiplied by 1.086, represents the weight of $C_{12}H_{17}N_2NaO_2S$ in the 10-ml. portion of the sample taken.

Packaging and storage—Preserve Sodium Thiamylal for Injection in *Containers for Sterile Solids* as described under *Injections,* page 810.

Labeling—Sodium Thiamylal for Injection complies with the requirements for *Labeling* under *Injections,* page 810.

Sizes available—Sodium Thiamylal for Injection is usually available in the following amounts: 500 mg.; 1, 5, and 10 g.

Category—General anesthetic.

Usual dose—Intravenous—Induction, **3** to **6 ml.** of 2.5 percent solution at the rate of **1 ml.** every 5 seconds; maintenance, **0.5** to **1 ml.** as required.

Sodium Vinbarbital Injection

Sodium Vinbarbital Injection is a sterile solution of sodium vinbarbital in a suitable solvent. It contains not less than 90.0 percent and not more than 105.0 percent of the labeled amount of $C_{11}H_{15}N_2NaO_3$ (sodium vinbarbital).

Note: Solutions of sodium vinbarbital in water decompose on standing.

Identification—

A: A portion of the residue of vinbarbital obtained in the *Assay* responds to the *Identification tests* under *Vinbarbital,* page 756.

B: An approximately 1 in 100,000 solution of a portion of the residue of vinbarbital obtained in the *Assay* and dissolved in 0.1 *N* sodium hydroxide exhibits an absorbance maximum at 252 ± 2 mμ and a minimum at 233 ± 2 mμ.

pH, page 824—The pH of Sodium Vinbarbital Injection is between 8.0 and 10.0.

Other requirements—Sodium Vinbarbital Injection meets the requirements under *Injections,* page 810.

Assay—Transfer an accurately measured volume of Sodium Vinbarbital Injection, equivalent to about 500 mg. of sodium vinbarbital, to a 125-ml. separator, add 30 ml. of water and 10 ml. of diluted hydrochloric acid, extract with seven 20-ml. portions of ether, and filter the combined extracts through ether-washed cotton or other suitable filter into a tared beaker, and wash the separator and the filter with several small portions of ether. Evaporate the combined filtrate and washings with the aid of a current of warm air. Dry the residue at 105° for 30 minutes, cool, and weigh. The weight of the residue, multiplied by 1.098, represents the weight of $C_{11}H_{15}N_2NaO_3$ in the portion of the Injection taken.

Packaging and storage—Preserve Sodium Vinbarbital Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injection available—Sodium Vinbarbital Injection usually available contains the following amount of sodium vinbarbital: 60 mg. in 1 ml.

Category—Sedative.

Usual dose—Parenteral, **60 mg.**

Sorbate, Potassium, page 578

Sorbic Acid

$CH_3CH{=}CHCH{=}CHCOOH$

$C_6H_8O_2$ Mol. wt. 112.13

Sorbic Acid contains not less than 99.0 percent and not more than 101.0 percent of $C_6H_8O_2$, calculated on the anhydrous basis.

Description—Sorbic Acid occurs as a free-flowing white, crystalline powder, having a characteristic odor.

Solubility—Sorbic Acid is slightly soluble in water. It is soluble in alcohol and in ether.

Identification—

A: To a solution of 200 mg. of Sorbic Acid in 2 ml. of alcohol add a few drops of bromine T.S.: the color is discharged.

B: A 1 in 400,000 solution of Sorbic Acid in isopropyl alcohol exhibits an absorbance maximum at 254 ± 2 mμ.

Melting range, page 814—Sorbic Acid melts between 133° and 137°.

Residue on ignition, page 858—Sorbic Acid yields not more than 0.2 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Sorbic Acid is 10 parts per million.

Water, page 900—Determine the water content of Sorbic Acid by the titrimetric method: not more than 0.5 percent is found.

Assay—Dissolve about 250 mg. of Sorbic Acid, accurately weighed, in 50 ml. of anhydrous methanol which previously has been neutralized with 0.1 *N* sodium hydroxide. Add 3 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to the first pink color which persists for at least 30 seconds. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 11.21 mg. of $C_6H_8O_2$.

Packaging and storage—Preserve Sorbic Acid in tight containers.

CATEGORY—Preservative (antimicrobial).

Spearmint

Spearmint consists of the dried leaf and flowering top of *Mentha spicata* Linné (*Mentha viridis* Linné) (Common Spearmint) or of *Mentha cardiaca* Gerard ex Baker (Scotch Spearmint) (Fam. *Labiatæ*).

Unground Spearmint occurs more or less crumpled. The leaves are opposite, the blade is ovate-lanceolate and from 3 to 9 cm. in length with an acute or acuminate apex. The base of the leaf is narrowed or rounded and the margin is sharply and unequally serrate and bright green in color. Both surfaces are glabrous (*M. spicata*) or the lower surface shows a few hairs on the veins (*M. cardiaca*) and many amber-colored glandular hairs. The leaf is nearly sessile (*M. spicata*) or with a petiole less than 15 mm. in length (*M. cardiaca*). The stems of Spearmint are nearly glabrous and sometimes green, but generally dusky red or purplish in color, oppositely branched, quadrangular, ridged, and from 1 to 3 mm. in diameter. Verticillasters occur on more or less crowded or interrupted, lanceolate, nearly acute spikes, 3 to 9 mm. in diameter, and in fruit becoming 10 cm. in length (*M. spicata*) or in separated axillary clusters, each subtended by a pair of floral leaves resembling the foliage leaves in appearance but smaller, the inflorescence 5 to 14 mm. in diameter, and in fruit usually up to 15 cm. in length, occasionally up to 30 cm. (*M. cardiaca*). The bracts are linear-lanceolate, subulate, ciliate, 7 to 10 mm. in length, some of them longer than the flowers, subtending the flower clusters. The calyx is campanulate (*M. spicata*) to tubular-campanulate (*M. spicata*), subequally 5-toothed, glandular-punctate, pubescent on teeth, green (*M. spicata*) to purplish red (*M. cardiaca*). The corolla is glabrous, nearly white or from moderate yellowish brown to weak yellowish orange to pinkish to lilac and purple, tubular-campanulate, its tube shorter than the calyx (*M. spicata*) or longer (*M. cardiaca*), its limb 4-cleft. Stamens in fours are equal. The style is exserted, 2-cleft at the summit; nutlets are ellipsoidal, minutely grained (*M. spicata*) or warty (*M. cardiaca*), dark brown, and about 500 μ in diameter. The odor is aromatic, characteristic, and the taste is slightly pungent, characteristic, but not followed by a cooling sensation in the mouth.

Powdered Spearmint—Powdered Spearmint is green to olive-green and closely resembles powdered peppermint except for the absence of crystals from the globular heads of the glandular hairs and for the nonglandular hairs which are usually up to 6-celled.

Stems or other foreign organic matter, page 885—Spearmint contains not more than 2 percent of stems over 3 mm. in diameter, or other foreign organic matter.

CATEGORY—Flavor.

Spearmint Oil

Spearmint Oil is the volatile oil distilled with steam from the fresh, over-ground parts of the flowering plant of *Mentha spicata* Linné (*Mentha viridis* Linné) (Common Spearmint) or of *Mentha cardiaca* Gerard ex Baker (Scotch Spearmint) (Fam. *Labiatæ*). It contains not less than 55.0 percent, by volume, of $C_{10}H_{14}O$ (carvone).

Description—Spearmint Oil is a colorless, yellow, or greenish yellow liquid, having the characteristic odor and taste of spearmint.

Solubility in 80 percent alcohol—Spearmint Oil is soluble in one volume of 80 percent alcohol, but upon further dilution may become turbid.

Specific gravity, page 866—The specific gravity of Spearmint Oil is not less than 0.917 and not more than 0.934.

Angular rotation, page 822—The angular rotation of Spearmint Oil is between $-48°$ and $-59°$ in a 100-mm. tube.

Refractive index, page 858—The refractive index of Spearmint Oil is not less than 1.484 and not more than 1.491 at 20°.

Reaction—A solution of recently prepared Spearmint Oil in an equal volume of 80 percent alcohol is neutral or only slightly acid to moistened litmus.

Assay—Pipet 10.0 ml. of Spearmint Oil into a 100-ml. cassia flask, and add 50 ml. of a saturated solution of sodium sulfite, which has been neutralized to 2 drops of phenolphthalein T.S. with 30 percent sodium bisulfite solution. Heat the mixture in a bath of boiling water, and shake the flask repeatedly, neutralizing the mixture from time to time by the addition of a few drops of the 30 percent sodium bisulfite solution. When no coloration appears upon the addition of a few more drops of phenolphthalein T.S. and heating for 15 minutes, cool to room temperature, and when the liquids have separated completely, add sufficient of the sodium sulfite solution to raise the lower limit of the oily layer within the graduated portion of the neck. The oily layer measures not more than 4.5 ml., indicating the presence in the Oil of not less than 55.0 percent, by volume, of $C_{10}H_{14}O$.

Packaging and storage—Preserve Spearmint Oil in tight containers.

CATEGORY—Flavor.

Stannous Fluoride

SnF_2 Mol. wt. 156.69

Stannous Fluoride, dried at 105° for 4 hours, contains not less than 71.2 percent of Sn^{2+} (stannous tin), and not less than 22.3 percent and not more than 25.5 percent of F (fluoride).

Description—Stannous Fluoride occurs as a white, crystalline powder. It has a bitter, salty taste. It melts at about 213°.

Solubility—Stannous Fluoride is freely soluble in water, and is practically insoluble in alcohol, in ether, and in chloroform.

Identification—

A: Transfer 5 ml. of a solution of Stannous Fluoride (1 in 100) to a test tube, and add 2 ml. of calcium chloride T.S.: a fine, white precipitate of calcium fluoride appears.

B: Mix on a spot plate 2 drops of a solution of Stannous Fluoride (1 in 100) with 2 drops of silver nitrate T.S.: a brown-black precipitate is formed.

C: Add 1 drop of a solution of Stannous Fluoride (1 in 100) to 2 drops of mercuric chloride T.S.: a white, silky precipitate forms. Further addition of the solution of Stannous Fluoride gives a brown-black precipitate.

pH, page 824—The pH of a freshly prepared 0.4 percent solution of Stannous Fluoride is between 2.8 and 3.5.

Loss on drying, page 814—Dry Stannous Fluoride at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Water-insoluble substances—Transfer about 10 g. of Stannous Fluoride, accurately weighed, to a 400-ml. plastic beaker, add 200 ml. of water, and stir with a plastic rod for 3 minutes, or until no more solid dissolves. Filter through a tared porcelain filtering crucible tightly packed with asbestos fiber, and wash thoroughly, first with ammonium fluoride solution (1 in 100) and then with water. Dry the residue at 105° for 4 hours, cool, and weigh: the weight of the residue does not exceed 0.2 percent.

Antimony—

Rhodamine B solution—Dissolve 20 mg. of rhodamine B in 200 ml. of 0.5 *N* hydrochloric acid.

Standard preparation—Transfer 55.0 mg. of antimony potassium tartrate, accurately weighed, into a 200-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution into a 500-ml. volumetric flask, dilute to volume with dilute hydrochloric acid (1 in 2), and mix.

Test preparation—Transfer 1.0 g. of Stannous Fluoride, accurately weighed, into a 50-ml. volumetric flask, dilute to volume with dilute hydrochloric acid (1 in 2), and mix.

Procedure—Pipet 5.0 ml. each of the *Standard preparation* and of the *Test preparation* into separate 125-ml. separators, add 15 ml. of hydrochloric acid and 1 g. of ceric sulfate, and allow to stand for 5 minutes with occasional shaking. Add 500 mg. of hydroxylamine hydrochloride, and shake for 1 minute. Pipet 15.0 ml. of isopropyl ether into the mixture, shake for 30 seconds, add 7 ml. of water, and mix. Cool in a water bath for 10 minutes, shake for 30 seconds, allow the layers to separate, and discard the aqueous phase. Add 20 ml. of *Rhodamine B solution*, shake for 30 seconds, and discard the aqueous layer. Decant the ether layer from the top of the separator, centrifuge, if necessary, to obtain a clear solution, and concomitantly determine the absorbances of the solutions obtained from the *Test preparation* and from the *Standard preparation* at the maximum at about 550 mμ with a suitable spectrophotometer, using water as the blank: the absorbance of the *Test preparation* does not exceed that of the *Standard preparation* (50 parts per million).

Assay for stannous ion—Transfer to a 500-ml. conical flask 200 ml. of water and 100 ml. of hydrochloric acid, add a few boiling chips, and boil the mixture for 10 minutes, then add about 250 mg. of Stannous Fluoride, previously dried at 105° for 4 hours and accurately weighed. While passing a stream of an oxygen-free inert gas over the surface of the liquid, swirl the flask to dissolve the Stannous Fluoride and cool the solution to room temperature. Add 5 ml. of potassium iodide T.S., and titrate in an inert atmosphere with 0.1 *N* potassium iodate, adding starch T.S. as the end-point is neared. Each ml. of 0.1 *N* potassium iodate is equivalent to 5.935 mg. of Sn^{2+}.

Assay for fluoride—

Solution A—Dissolve 3.16 g. of 4,5-dihydroxy-3-(*p*-sulfophenylazo)-2,7-naphthalenedisulfonic acid trisodium salt in 550 ml. of water.

Solution B—Transfer to a 500-ml. volumetric flask 113 mg. of zirconium oxychloride and dissolve in 50 ml. of water. Add 350 ml. of hydrochloric acid, dilute to volume with water, and mix.

Solution C—Dilute 50 ml. of *Solution A* with 500 ml. of water and 35 ml. of hydrochloric acid. This solution is stable.

Solution D—Mix equal volumes of *Solution A* and *Solution B*, and store in an amber bottle.

Solution E—Dilute 10.0 ml. of *Solution D* to 100.0 ml. with water.

Standard preparation—Prepare, by quantitative and stepwise dilution, an aqueous solution of NF Sodium Fluoride Reference Standard, previously dried at 150° to constant weight, containing 10 mcg. of fluoride per ml.

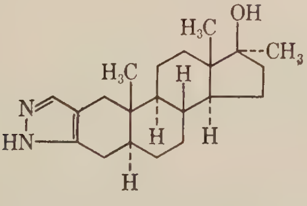
Assay preparation—Transfer to a 250-ml. volumetric flask about 100 mg. of Stannous Fluoride, previously dried at 105° for 4 hours and accurately weighed. Add 50 ml. of water, mix vigorously for 5 minutes, dilute to volume with water, and mix. Pipet 5.0 ml. of this solution into a 100-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Pipet into individual 100-ml. volumetric flasks, 1.0, 2.0, 3.0, and 4.0 ml. of the *Standard preparation*, and pipet into another 100-ml. volumetric flask 5.0 ml. of the *Assay preparation*. Add 10.0 ml. of *Solution D* to each flask, dilute to volume with water, and mix. By means of a suitable spectrophotometer, determine the absorbances of *Solution E* and the fluoride-containing solutions at the maximum at about 590 mμ, using *Solution C* as the blank. Subtract the absorbances obtained with the fluoride-containing solutions from the absorbance obtained with *Solution E*. Prepare a standard curve by plotting the amount of fluoride added, in mcg., against the absorbance differences. From the standard curve, determine the concentration, in mcg. per 5 ml., of F in the *Assay preparation*. This value is equal to the quantity, in mg., of F in the portion of Stannous Fluoride taken.

Packaging and storage—Preserve Stannous Fluoride in well-closed containers.

Category—Dental caries prophylactic.
Application—Topically to the teeth.

Stanozolol*



17-Methyl-2′*H*-5α-androst-2-eno[3,2-*c*]pyrazol-17β-ol

$C_{21}H_{32}N_2O$ Mol. wt. 328.50

Stanozolol contains not less than 98.0 percent and not more than 100.5 percent of $C_{21}H_{32}N_2O$, calculated on the dried basis.

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* Patented. See notice, page ii.

Description—Stanozolol occurs as an odorless, crystalline powder. The powder occurs in two forms: as needles, melting within the range of about 153° to 156°, and as prisms, melting within the range of about 230° to 242°.

Solubility—Stanozolol is insoluble in water. It is soluble in dimethylformamide, sparingly soluble in alcohol and in chloroform, slightly soluble in ethyl acetate and in acetone, and very slightly soluble in benzene.

Identification—Boil about 2 mg. of Stanozolol with 5 ml. of benzene, filter, and evaporate to dryness on a steam bath. To the residue add 3 ml. of *p*-dimethylaminobenzaldehyde T.S.: a yellow color develops which exhibits a green fluorescence when viewed under longwave ultraviolet light.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Stanozolol, previously dried at 100° to constant weight at a pressure not exceeding 5 mm. of mercury, exhibits maxima only at the same wavelengths as that of NF Stanozolol Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 20,000 solution of Stanozolol in alcohol exhibits maxima and minima at the same wavelengths as that of NF Stanozolol Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 224 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Stanozolol, determined in a solution in chloroform containing 100 mg. of Stanozolol in each 10 ml., calculated on the dried basis, is between +34° and +40°.

Loss on drying, page 814—Dry Stanozolol at 100° to constant weight at a pressure not exceeding 5 mm. of mercury: it loses not more than 1 percent of its weight.

Assay—Dissolve 700 mg. of Stanozolol in 50 ml. of glacial acetic acid, add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 32.85 mg. of $C_{21}H_{32}N_2O$.

Packaging and storage—Preserve Stanozolol in tight, light-resistant containers.

CATEGORY—Androgen.
USUAL DOSE—**2 mg.** three times a day.

Stanozolol Tablets

Stanozolol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{32}N_2O$.

Identification—An amount of powdered Stanozolol Tablets, equivalent to about 2 mg. of stanozolol, responds to the *Identification test* under *Stanozolol,* page 665.

Disintegration, page 878—The disintegration time limit for Stanozolol Tablets is 15 minutes.

Content uniformity, *Method I,* page 799—Stanozolol Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Transfer about 25 mg. of NF Stanozolol Reference Standard, accurately weighed, to a 50-ml. volumetric flask, add glacial acetic acid to volume, and mix.

Assay preparation—Weigh and finely powder not less than 20 Stanozolol Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 25 mg. of stanozolol, to a 50-ml. volumetric flask, add 30 ml. of glacial acetic acid, and heat on a steam bath for 10 minutes, shaking continuously. Cool, dilute to volume with glacial acetic acid, and mix. Filter, discarding the first 10 ml. of filtrate, and use the subsequent filtrate as directed in the *Procedure.*

Procedure—Transfer 4.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 25-ml. volumetric flasks, and transfer 4.0 ml. of glacial acetic acid to a third flask to serve as the blank. To each flask add 1.0 ml. of a 1 in 10 solution of *m*-nitrobenzaldehyde in glacial acetic acid and 1.0 ml. of a 1 in 10 solution of perchloric acid in glacial acetic acid, then dilute to 20 ml. with glacial acetic acid, and heat in a boiling water bath for 45 minutes. Cool, dilute to volume with glacial acetic acid, and mix. Concomitantly determine the absorbance of the solutions, in 1-cm. cells, at the maximum at about 380 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{32}N_2O$ in the portion of the Tablets taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Stanozolol Tablets in tight, light-resistant containers.

Tablets available—Stanozolol Tablets usually available contain the following amount of stanozolol: 2 mg.

CATEGORY and DOSE—See Stanozolol.

Starch Glycerite

Starch	**100 g.**
Benzoic Acid	**2 g.**
Purified Water	**200 ml.**
Glycerin	**700 ml.**
To make about	**1000 g.**

Rub the starch and the benzoic acid with the purified water in a porcelain dish until a smooth mixture is produced, then add the glycerin, and mix well. Heat the mixture on a sand bath to a temperature between 140° and 144°, with constant but gentle stirring until a translucent, jelly-like mass results, and then strain through muslin.

Starch Glycerite should be freshly prepared.

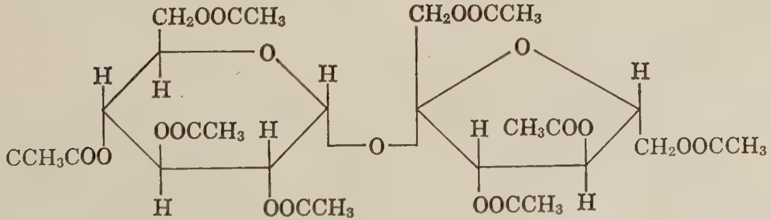
Packaging and storage—Preserve Starch Glycerite in tight containers.

CATEGORY—Emollient.

FOR EXTERNAL USE—Topically as required.

Stearate, Calcium, page 130
Stearate, Sodium, page 660
Sterile Betamethasone Sodium Phosphate and Betamethasone Acetate Suspension, page 91
Sterile Chloramphenicol for Suspension, page 147
Sterile Chymotrypsin, page 169
Sterile Desoxycorticosterone Pivalate Suspension, page 207
Sterile Estradiol Suspension, page 279
Sterile Methacholine Chloride, page 421
Sterile Methylprednisolone Acetate Suspension, page 452
Sterile Oleandomycin Phosphate, page 496
Sterile Progesterone Suspension, page 599
Sterile Testosterone Suspension, page 689
Sterile Triamcinolone Diacetate Suspension, page 717
Strong Ammonia Solution, page 41
Stronger Rose Water, page 626
Sublimed Sulfur, page 680

Sucrose Octaacetate



$C_{28}H_{38}O_{19}$ Mol. wt. 678.60

Sucrose Octaacetate contains not less than 98.0 percent and not more than 100.5 percent of $C_{28}H_{38}O_{19}$, calculated on the anhydrous basis.

Description—Sucrose Octaacetate occurs as a white, practically odorless powder having an intensely bitter taste. It is hygroscopic.

Solubility—Sucrose Octaacetate is very soluble in methanol and in chloroform, and is soluble in alcohol and in ether. It is very slightly soluble in water.

Melting temperature, page 814—Sucrose Octaacetate melts at a temperature not lower than 78°.

Acidity—Dissolve 1 g. of Sucrose Octaacetate in 20 ml. of neutralized alcohol, and add 2 drops of phenolphthalein T.S.: not more than 2 drops of 0.1 *N* sodium hydroxide are required to produce a red color.

Water, page 900—Determine the water content of Sucrose Octaacetate by the titrimetric method: not more than 1 percent is found.

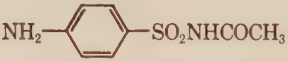
Residue on ignition, page 858—Sucrose Octaacetate yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 100 mg. of Sucrose Octaacetate, accurately weighed, into a 500-ml. conical flask and dissolve in about 50 ml. of 70 percent alcohol. Neutralize the solution with 0.1 *N* sodium hydroxide, using phenolphthalein T.S. as the indicator. Add 25.0 ml. of 0.1 *N* sodium hydroxide, attach an air condenser to the flask, and reflux on a steam bath for 1 hour. Remove from the steam bath, cool quickly, and titrate the excess alkali with 0.1 *N* sulfuric acid, using phenolphthalein T.S. as the indicator. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* sodium hydroxide is equivalent to 8.483 mg. of $C_{28}H_{38}O_{19}$.

Packaging and storage—Preserve Sucrose Octaacetate in tight containers.

CATEGORY—Alcohol denaturant.

Sulfacetamide



N-Sulfanilylacetamide

$C_8H_{10}N_2O_3S$ Mol. wt. 214.24

Sulfacetamide, dried at 105° for 2 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_8H_{10}N_2O_3S$.

Description—Sulfacetamide occurs as a white, crystalline powder. It is odorless and has a characteristic, sour taste.

Solubility—Sulfacetamide is slightly soluble in water. It is soluble in alcohol, slightly soluble in ether, very slightly soluble in chloroform, and practically insoluble in benzene. It is freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides. Solutions of Sulfacetamide are sensitive to light, and are unstable when acidic or strongly alkaline.

Identification—

A: Place about 500 mg. of Sulfacetamide in a test tube, heat gently until it boils, and cool. An oily liquid, which has the characteristic odor of acetamide, condenses on the walls of the test tube (*distinction from the sublimates of sulfadiazine, sulfamerazine, sulfamethazine, and sulfapyrazine, which are solids at room temperature*).

B: To about 100 mg. of Sulfacetamide add 5 ml. of water followed by sodium hydroxide T.S., added dropwise, with shaking, to effect solution. Add 5 drops of cupric sulfate T.S.: a light bluish green precipitate forms, which remains unchanged on standing.

Melting range, page 814—Sulfacetamide melts between 181° and 184°.

Clarity and color of solution—Dissolve about 200 mg. of Sulfacetamide in 5 ml. of sodium hydroxide T.S.: the solution is yellow to faintly yellow without more than a trace of turbidity.

Reaction—An aqueous solution of Sulfacetamide (1 in 150) is acid to litmus.

Loss on drying, page 814—Dry Sulfacetamide at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Sulfacetamide yields not more than 0.1 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 200 mg. of Sulfacetamide meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Sulfate, page 784—Digest 1 g. of Sulfacetamide with 50 ml. of water at about 70° for 5 minutes. Cool at once to room temperature, and filter. A 25-ml. portion of the filtrate shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (0.04 percent).

Heavy metals, page 806—Dissolve 1 g. of Sulfacetamide in 5 ml. of sodium hydroxide T.S., and add 20 ml. of water and 5 drops of freshly prepared sodium sulfide T.S.: any darkening produced does not exceed that produced in a blank made with the same quantities of the same reagents and to which 2 ml. of standard lead solution has been added (20 parts per million).

Assay—Transfer about 500 mg. of Sulfacetamide, previously dried at 105° for 2 hours and accurately weighed, to a beaker or a casserole. Add 20 ml. of hydrochloric acid and 50 ml. of water, cool to 15°, and slowly titrate with 0.1 *M* sodium nitrite determining the end-point electrometrically by means of suitable electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 21.42 mg. of $C_8H_{10}N_2O_3S$.

Packaging and storage—Preserve Sulfacetamide in well-closed, light-resistant containers.

CATEGORY—Antibacterial.

USUAL DOSE—Initial, **4 g.** Maintenance, **1 g.** every 4 hours.

Sulfacetamide Tablets

Sulfacetamide Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_{10}N_2O_3S$.

Identification—Reflux a quantity of finely powdered Sulfacetamide Tablets, equivalent to about 1.5 g. of sulfacetamide, with 30 ml. of acetone for 10 minutes, filter the mixture, and evaporate the filtrate to dryness on a steam bath: the residue, crystallized from 25 ml. of water and dried at 105° for 4 hours, melts between 180° and 184°, page 814, and responds to the *Identification tests* under *Sulfacetamide,* page 668.

Disintegration, page 878—The disintegration time limit for Sulfacetamide Tablets is 15 minutes.

Weight variation, page 901—Sulfacetamide Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Sulfacetamide Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg. of sulfacetamide, transfer it to a beaker or a casserole, and proceed as directed in the *Assay* under *Sulfacetamide,* page 668, beginning with "Add 20 ml. of hydrochloric acid . . . ."

Packaging and storage—Preserve Sulfacetamide Tablets in well-closed, light-resistant containers.

Tablets available—Sulfacetamide Tablets usually available contain the following amount of sulfacetamide: 500 mg.

CATEGORY and DOSE—See Sulfacetamide.

Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension

Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_8H_{10}N_2O_3S$ (sulfacetamide), of $C_{10}H_{10}N_4O_2S$ (sulfadiazine), and of $C_{11}H_{12}N_4O_2S$ (sulfamerazine), in a buffered, aqueous suspension.

Identification—

A: Sulfacetamide: Dilute 10 ml. of Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension to 100 ml. with water, add 10 ml. of sodium hydroxide solution (1 in 10), and when the resulting mixture is clear or nearly so, add 16 ml. of 1.66 *N* acetic acid. Mix well and filter. To 5 ml. of the filtrate add sufficient sodium hydroxide T.S. to render it alkaline to litmus, and add 5 drops of cupric sulfate T.S.: a characteristic light bluish green precipitate forms which remains unchanged on standing.

B: Sulfadiazine: The R_f value, page 789, determined from the paper strips used in the *Assay* is between 0.16 and 0.20.

C: Sulfamerazine: The R_f value, page 789, determined from the paper strips used in the *Assay* is between 0.26 and 0.31.

Assay for sulfacetamide—To 10.0 ml. of the Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension in a 100-ml. beaker add 10 ml. of water and 10 ml. of sodium hydroxide solution (1 in 10), and stir until solution is complete or nearly so. Adjust the pH to 6.0 with 1.66 *N* acetic acid, let stand for 5 minutes, collect the precipitate, consisting of sulfadiazine and sulfamerazine, on a medium-porosity, sintered-glass funnel, and wash it with 10 ml. of 0.166 *N* acetic acid. To the combined filtrate and washings add 15 ml. of hydrochloric acid, and cool to 15°. Titrate slowly with 0.1 *M* sodium nitrite, determining the end-point electrometrically by means of suitable electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 21.42 mg. of $C_8H_{10}N_2O_3S$.

Assay for sulfadiazine and sulfamerazine—Proceed as directed under *Sulfonamides*, page 877, using the following as the *Assay preparation:* Dissolve the precipitate of sulfadiazine and sulfamerazine obtained in the *Assay for sulfacetamide* in 10 ml. of stronger ammonia water and 10 ml. of water. Transfer the resulting solution to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer an accurately measured volume of the solution, equivalent to 25 mg. each of sulfadiazine and sulfamerazine, to a 25-ml. volumetric flask, dilute to volume with methanol, and mix.

Packaging and storage—Preserve Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension in tight, light-resistant containers.

Suspension available—Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension usually available contains 167 mg. of each sulfonamide in each 5 ml.

CATEGORY—Antibacterial.

USUAL DOSE OF COMBINATIONS OF SULFACETAMIDE, SULFADIAZINE, AND SULFAMERAZINE—Initial, **4 g.,** then **500 mg.** to **1 g.** every 4 hours.

Sulfacetamide, Sulfadiazine, and Sulfamerazine Tablets

Sulfacetamide, Sulfadiazine, and Sulfamerazine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_8H_{10}N_2O_3S$ (sulfacetamide), $C_{10}H_{10}N_4O_2S$ (sulfadiazine), and $C_{11}H_{12}N_4O_2S$ (sulfamerazine).

Identification—

A: Sulfacetamide: To a finely powdered portion of Sulfacetamide, Sulfadiazine, and Sulfamerazine Tablets, equivalent to about 1.5 g. of total sulfonamides, add 20 ml. of water and 10 ml. of sodium hydroxide solution (1 in 10). Stir the mixture until solution is complete or nearly so, add 16 ml. of 1.66 *N* acetic acid, let stand for 5 minutes, and filter through a medium-porosity, sintered-glass funnel. To 5 ml. of the filtrate add sufficient sodium hydroxide T.S. to render it alkaline to litmus, and add 5 drops of cupric sulfate T.S.: a characteristic light bluish green precipitate forms, which remains unchanged on standing.

B: Sulfadiazine: The R_f value, page 789, determined from the paper strips used in the *Assay*, is between 0.16 and 0.20.

C: Sulfamerazine: The R_f value, page 789, determined from the paper strips used in the *Assay*, is between 0.26 and 0.31.

Disintegration, page 878—The disintegration time limit for Sulfacetamide, Sulfadiazine, and Sulfamerazine Tablets is 30 minutes.

Weight variation, page 901—Sulfacetamide, Sulfadiazine, and Sulfamerazine Tablets meet the requirements of the weight variation test for tablets.

Assay for sulfacetamide—Weigh and finely powder not less than 20 Sulfacetamide, Sulfadiazine, and Sulfamerazine Tablets. Weigh accurately a portion of the powder, equivalent to about 1.5 g. of total sulfonamides, transfer to a 100-ml. beaker, and add 20 ml. of water and 10 ml. of ammonia T.S. Stir until solution is complete or nearly so. Then proceed as directed in the *Assay for sulfacetamide* under *Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension*, page 699, beginning with "Adjust the pH to 6.0 with 1.66 *N* acetic acid . . . ."

Assay for sulfadiazine and sulfamerazine—Proceed as directed in the *Assay for sulfadiazine and sulfamerazine* under *Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension*, page 699.

Packaging and storage—Preserve Sulfacetamide, Sulfadiazine, and Sulfamerazine Tablets in well-closed, light-resistant containers.

Tablets available—Sulfacetamide, Sulfadiazine, and Sulfamerazine Tablets usually available contain 167 mg. each of sulfacetamide, sulfadiazine, and sulfamerazine.

CATEGORY and DOSE—See Sulfacetamide, Sulfadiazine, and Sulfamerazine Oral Suspension.

Sulfadiazine and Sulfamerazine Tablets

Sulfadiazine and Sulfamerazine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_{10}H_{10}N_4O_2S$ (sulfadiazine) and $C_{11}H_{12}N_4O_2S$ (sulfamerazine).

Identification—

A: Sulfadiazine: The R_f value, page 789, determined from the paper strips used in the *Assay* is between 0.16 and 0.20.

B: Sulfamerazine: The R_f value, page 789, determined from the paper strips used in the *Assay* is between 0.26 and 0.31.

Disintegration, page 878—The disintegration time limit for Sulfadiazine and Sulfamerazine Tablets is 30 minutes.

Weight variation, page 901—Sulfadiazine and Sulfamerazine Tablets meet the requirements of the weight variation test for tablets.

Assay—Proceed as directed under *Sulfonamides*, page 877, using the following as the *Assay Preparation:* Weigh and finely powder not less than 20 Sulfadiazine and Sulfamerazine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg. of each sulfonamide, to a 50-ml. volumetric flask containing 3 ml. of stronger ammonia water, add 25 ml. of methanol, shake occasionally for 15 minutes, dilute to volume with methanol, and mix.

Packaging and storage—Preserve Sulfadiazine and Sulfamerazine Tablets in well-closed, light-resistant containers.

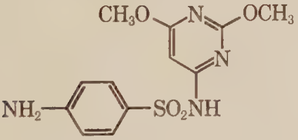
Tablets available—Sulfadiazine and Sulfamerazine Tablets usually available contain the following amounts of sulfadiazine and sulfamerazine: of each 250 mg.

CATEGORY—Antibacterial.

USUAL DOSE OF COMBINED SULFADIAZINE AND SULFAMERAZINE—Initial, **4 g.,** then **2 g.** every 4 hours.

Sulfadiazine, Sulfamerazine and Sulfacetamide Oral Suspension, page 669
Sulfadiazine, Sulfamerazine and Sulfacetamide Tablets, page 670

Sulfadimethoxine*



N^1-(2,6-Dimethoxy-4-pyrimidinyl)sulfanilamide

$C_{12}H_{14}N_4O_4S$ Mol. wt. 310.33

Sulfadimethoxine, dried at 105° for 3 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_{12}H_{14}N_4O_4S$.

Description—Sulfadimethoxine occurs as a practically white, odorless, crystalline powder.

Solubility—Sulfadimethoxine is slightly soluble in alcohol and is sparingly soluble in 2 *N* hydrochloric acid. It is practically insoluble in water. It is slightly soluble in ether, in chloroform, and in solvent hexane. It is readily soluble in 2 *N* sodium hydroxide.

Identification—

A: To about 100 mg. of Sulfadimethoxine, add 3 ml. of sodium hydroxide solution (1 in 10) and 50 ml. of water, mix until dissolved, and dilute to 100 ml. To about 5 ml. of this solution, add 100 mg. of phenol, and heat to boiling. Cool the solution, add 0.5 ml. of sodium hypochlorite solution (about 17 percent available Cl) and 3 drops of sodium hydroxide solution (1 in 10): a yellow color is produced.

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* Patented. See notice, page ii.

B: To a suspension of about 20 mg. of Sulfadimethoxine in 5 ml. of water add sodium hydroxide T.S. until completely dissolved. Add 3 drops of cupric sulfate T.S.: the solution turns yellow and a yellow precipitate is formed.

C: To about 10 mg. of Sulfadimethoxine dissolved in 2 ml. of diluted hydrochloric acid add 3 drops of sodium nitrite solution (1 in 100), and dilute to 4 ml. with water: a yellow solution is produced. Add 1 ml. of sodium hydroxide solution (1 in 10) containing 10 mg. of betanaphthol: a red-orange precipitate is formed.

Melting range, page 814—Sulfadimethoxine melts between 197° and 202°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of sulfadimethoxine, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Sulfadimethoxine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Sulfadimethoxine in alcohol exhibits maxima and minima at the same wavelengths as that of NF Sulfadimethoxine Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis at the point of maximum absorbance at about 272 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Sulfadimethoxine at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Sulfadimethoxine yields not more than 0.1 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 200 mg. of Sulfadimethoxine meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Heavy metals, *Method II,* page 806—The heavy metals limit for Sulfadimethoxine is 20 parts per million.

Assay—Weigh accurately about 500 mg. of Sulfadimethoxine, previously dried at 105° for 3 hours, and transfer it to a 250-ml. beaker. Add 40 ml. of hydrochloric acid, stir until dissolved, warming if necessary, add 10 ml. of glacial acetic acid and 50 ml. of water, cool to room temperature, and slowly titrate with 0.1 *M* sodium nitrite, determining the end-point electrometrically by means of suitable electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 31.03 mg. of $C_{12}H_{14}N_4O_4S$.

Packaging and storage—Preserve Sulfadimethoxine in well-closed, light-resistant, containers.

CATEGORY—Antibacterial.

USUAL DOSE—Initial, **2 g.**, then **1 g.** daily.

USUAL DOSE RANGE—**500 mg.** to **1 g.**

Sulfadimethoxine Oral Suspension

Sulfadimethoxine Oral Suspension contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{12}H_{14}N_4O_4S$, in a buffered aqueous suspension.

Identification—Dilute 1 ml. of Sulfadimethoxine Oral Suspension with 50 ml. of water, add sodium hydroxide solution (1 in 10), dropwise, until the solution becomes clear, then add diluted hydrochloric acid, dropwise, until a precipitate forms. Collect the precipitate on a filter, wash it with water and with ether: the sulfadimethoxine so obtained responds to *Identification tests B* and *C* under *Sulfadimethoxine,* page 671.

Assay—Transfer to a beaker an accurately measured volume of Sulfadimethoxine Oral Suspension, equivalent to about 500 mg. of sulfadimethoxine, and proceed as directed in the *Assay* under *Sulfadimethoxine,* page 671, beginning with "Add 40 ml. of hydrochloric acid . . . ."

Packaging and storage—Preserve Sulfadimethoxine Oral Suspension in tight, light-resistant containers.

Suspension available—Sulfadimethoxine Oral Suspension usually available contains the following amount of sulfadimethoxine: 250 mg. in 5 ml.

CATEGORY and DOSE—See Sulfadimethoxine.

Sulfadimethoxine Tablets

Sulfadimethoxine Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{12}H_{14}N_4O_4S$.

Identification—Shake a quantity of finely powdered Sulfadimethoxine Tablets, equivalent to about 1 g. of sulfadimethoxine, with 5 ml. of diluted hydrochloric acid and 10 ml. of water. Filter, and to the filtrate add, dropwise, sodium hydroxide solution (1 in 10) until a precipitate forms, and redissolves. Add diluted hydrochloric acid, dropwise, until a precipitate forms. Collect the precipitate on a very fine filter, wash it with water and with ether: the sulfadimethoxine so obtained responds to *Identification tests B* and *C* under *Sulfadimethoxine*, page 671.

Disintegration, page 878—The disintegration time limit for Sulfadimethoxine Tablets is 30 minutes.

Weight variation, page 901—Sulfadimethoxine Tablets meet the requirements of the weight variation test for tablets.

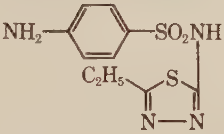
Assay—Weigh and finely powder not less than 20 Sulfadimethoxine Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg. of sulfadimethoxine, and transfer it to a beaker. Proceed as directed in the *Assay* under *Sulfadimethoxine*, page 671, beginning with "Add 40 ml. of hydrochloric acid . . . ."

Packaging and storage—Preserve Sulfadimethoxine Tablets in well-closed, light-resistant containers.

Tablets available—Sulfadimethoxine Tablets usually available contain the following amounts of sulfadimethoxine: 250 and 500 mg.

Category and Dose—See Sulfadimethoxine.

Sulfaethidole



N^1-(5-Ethyl-1,3,4-thiadiazol-2-yl)sulfanilamide

$C_{10}H_{12}N_4O_2S_2$ Mol. wt. 284.36

Sulfaethidole, dried at 105° for 2 hours, contains not less than 98.5 percent and not more than 100.5 percent of $C_{10}H_{12}N_4O_2S_2$.

Description—Sulfaethidole occurs as a white to yellowish white, practically odorless, crystalline powder.

Solubility—Sulfaethidole is very slightly soluble in water, in benzene, in chloroform, and in ether. It is sparingly soluble in alcohol. It is slightly soluble in dilute mineral acids and is freely soluble in solutions of fixed alkali hydroxides.

Identification—

A: To about 100 mg. of Sulfaethidole add 5 ml. of diluted hydrochloric acid, and boil gently for about 5 minutes. Cool in an ice bath, then add 4 ml. of a solution of sodium nitrite (1 in 100), add water to make 10 ml., and cool the mixture in an ice bath for 10 minutes. To 5 ml. of the mixture add a solution of 50 mg. of betanaphthol in 2 ml. of sodium hydroxide solution (1 in 10): an orange-red precipitate is formed which darkens on standing.

B: To a suspension of about 20 mg. of Sulfaethidole in 5 ml. of water add sufficient sodium hydroxide T.S. to dissolve the sample, and then add 2 drops of cupric sulfate T.S.: a light green precipitate is formed which does not change on standing.

Melting range, page 814—Sulfaethidole melts between 186° and 190°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Sulfaethidole, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Sulfaethidole Reference Standard, similarly measured.

pH, page 824—The pH of a suspension of Sulfaethidole (1 in 100) is between 4.4 and 4.9.

Loss on drying, page 814—Dry Sulfaethidole at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Selenium—A *Test preparation* prepared with 200 mg. of Sulfaethidole meets the requirements of the *Selenium Limit Test*, page 865 (30 parts per million).

Heavy metals, *Method II*, page 806—The heavy metals limit for Sulfaethidole is 20 parts per million.

Assay—Transfer about 500 mg. of Sulfaethidole, previously dried at 105° for 2 hours and accurately weighed, to a beaker or a casserole. Add 20 ml. of hydrochloric acid and 50 ml. of water, stir until dissolved, cool to 15°, and slowly titrate with 0.1 *M* sodium nitrite, determining the end-point electrometrically by means of suitable electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 28.44 mg. of $C_{10}H_{12}N_4O_2S_2$.

Packaging and storage—Preserve

Sulfaethidole in well-closed, light-resistant containers.

Category—Antibacterial.

Usual dose—Initial, **2.6 g.**, then **1.3 g.** every 12 hours.

Usual dose range—**1.3** to **3.9 g.** daily.

Sulfamerazine Tablets

Sulfamerazine Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{11}H_{12}N_4O_2S$.

Identification—

A: Triturate a quantity of finely powdered Sulfamerazine Tablets, equivalent to about 500 mg. of sulfamerazine, with two 5-ml. portions of chloroform, and discard the chloroform. Triturate the residue with 10 ml. of sodium hydroxide T.S. for 5 minutes, then add 10 ml. of water, and filter. To the filtrate add, with stirring, acetic acid until the mixture is distinctly acid: a white precipitate is formed. Collect the precipitate on a filter, wash it well with cold water, and dry at 105° for 1 hour: the sulfamerazine so obtained melts between 233° and 238°, page 814, and responds to *Identification tests B* and *C*.

B: To about 20 mg. of the sulfamerazine obtained in *Identification test A*, add 5 ml. of water, shake well, and add sodium hydroxide T.S., dropwise, until dissolved, then add 2 or 3 drops of cupric sulfate T.S.: an olive-green precipitate forms which becomes dark gray on standing.

C: The infrared absorption spectrum of a potassium bromide dispersion of the sulfamerazine obtained in *Identification test A* exhibits maxima at the same wavelengths as that of USP Sulfamerazine Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Sulfamerazine Tablets is 30 minutes.

Weight variation, page 901—Sulfamerazine Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Sulfamerazine Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg. of sulfamerazine, and transfer it to a beaker or casserole. Add 50 ml. of water and 20 ml. of hydrochloric acid, stir until dissolved, cool to 15°, add about 25 g. of crushed ice, and slowly titrate with 0.1 *M* sodium nitrite, stirring vigorously, until a blue color is produced immediately when the titrated solution is spotted on starch iodide paper. When the titration is complete, the endpoint is reproducible after the mixture has been allowed to stand for 1 minute. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 26.43 mg. of $C_{11}H_{12}N_4O_2S$.

Packaging and storage—Preserve Sulfamerazine Tablets in well-closed containers.

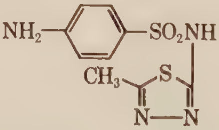
Tablets available—Sulfamerazine Tablets usually available contain the following amount of sulfamerazine: 500 mg.

Category—Antibacterial.

Usual dose of sulfamerazine—Initial, **4 g.** Maintenance, **1 g.** every six hours.

Sulfamerazine and Sulfadiazine Tablets, page 671
Sulfamerazine, Sulfadiazine and Sulfacetamide Oral Suspension, page 669
Sulfamerazine, Sulfadiazine and Sulfacetamide Tablets, page 670

Sulfamethizole



N^1-(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanilamide

$C_9H_{10}N_4O_2S_2$ Mol. wt. 270.33

Sulfamethizole, dried at 105° for 2 hours, contains not less than 99.0 percent and not more than 100.5 percent of $C_9H_{10}N_4O_2S_2$.

Description—Sulfamethizole occurs as white crystals or powder. It has a slightly bitter taste and is almost odorless; it has no odor of hydrogen sulfide.

Solubility—Sulfamethizole is very slightly soluble in water. It is freely soluble in solutions of ammonium, potassium, and sodium hydroxides, and is soluble in dilute mineral acids. It is soluble in acetone, sparingly soluble in alcohol, very slightly soluble in chloroform and in ether, and practically insoluble in benzene.

Identification—

A: To 100 mg. of Sulfamethizole add 5 ml. of diluted hydrochloric acid, and boil gently for about 5 minutes. Cool in an ice bath, then add 4 ml. of a solution of sodium nitrite (1 in 100), add water to make 10 ml., and place the mixture in an ice bath for 10 minutes. To 5 ml. of the cooled mixture, add a solution of 50 mg. of beta-naphthol in 2 ml. of sodium hydroxide solution (1 in 10): an orange-red precipitate is formed which darkens on standing.

B: To about 20 mg. of Sulfamethizole suspended in 5 ml. of water add, dropwise, sodium hydroxide T.S. until dissolved, then add 2 or 3 drops of cupric sulfate T.S.: a light green precipitate forms which does not change on standing.

Melting range, page 814—Sulfamethizole melts between 209° and 212°.

Clarity and color of solution—Dissolve 1 g. of Sulfamethizole in 20 ml. of water and 5 ml. of sodium hydroxide T.S.: the solution is clear and not more than pale yellow.

Acidity—Digest 2 g. of Sulfamethizole with 100 ml. of water at about 70° for 5 minutes, cool at once to about 20°, and filter. To 25 ml. of the filtrate add 2 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide: not more than 0.5 ml. is required for neutralization. Save the remainder of the filtrate.

Loss on drying, page 814—Dry Sulfamethizole at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Sulfamethizole yields not more than 0.1 percent of residue on ignition.

Chloride, page 784—A 25-ml. portion of the filtrate prepared in the test for *Acidity* shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (0.014 percent).

Selenium—A *Test Preparation* prepared with 200 mg. of Sulfamethizole meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Sulfate, page 784—A 25-ml. portion of the filtrate prepared in the test for *Acidity* shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (0.04 percent).

Heavy metals, page 806—Dissolve 500 mg. of Sulfamethizole in a mixture of 5 ml. of sodium hydroxide T.S. and 20 ml. of water, and to the solution add 5 drops of sodium sulfide T.S.: any darkening produced does not exceed that of a blank to which 1 ml. of standard lead solution has been added (20 parts per million).

Assay—Weigh accurately about 500 mg. of Sulfamethizole, previously dried at 105° for 2 hours, and transfer it to a beaker or casserole. Add 50 ml. of water and 20 ml. of hydrochloric acid, stir until dissolved, cool to 15°, and slowly titrate with 0.1 *M* sodium nitrite, determining the end-point electrometrically by means of suitable electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 27.03 mg. of $C_9H_{10}N_4O_2S_2$.

Packaging and storage—Preserve Sulfamethizole in well-closed, light-resistant containers.

CATEGORY—Antibacterial.
USUAL DOSE—**500 mg.** four times daily.
USUAL DOSE RANGE—**500 mg.** to **1 g.**

Sulfamethizole Oral Suspension

Sulfamethizole Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{10}N_4O_2S_2$, in a buffered aqueous suspension.

Identification—Place a quantity of Sulfamethizole Oral Suspension, equivalent to about 500 mg. of sulfamethizole, in a 50-ml. centrifuge tube, add about 30 ml. of water, mix thoroughly, and centrifuge the mixture. Decant and discard the supernatant liquid. Resuspend the residue in 15 ml. of water, mix thoroughly, and centrifuge the mixture. Decant and discard the clear, supernatant liquid. Repeat the washing procedure an additional two times. Dissolve the residue in 10 ml. of ammonia T.S. and 10 ml. of water, and filter. Warm the filtrate until most of the ammonia is expelled, cool, and add acetic acid until the mixture is distinctly acid: a precipitate of sulfamethizole is formed. Collect the precipitate on a filter, wash it well with cold water, and dry at 105° for 1 hour: the sulfamethizole so obtained melts between 209° and 212°, page 814, and responds to the *Identification tests* under *Sulfamethizole,* page 674.

Assay—Transfer to a beaker or casserole an accurately measured volume of Sulfamethizole Suspension, equivalent to about 500 mg. of sulfamethizole, and proceed as directed in the *Assay* under *Sulfamethizole,* page 674, beginning with "... Add 50 ml. of water and 20 ml. of hydrochloric acid . . . ."

Packaging and storage—Preserve Sulfamethizole Oral Suspension in tight, light-resistant containers.

Suspension available—Sulfamethizole Oral Suspension usually available contains 250 mg. of sulfamethizole in each 5 ml.

Category and Dose—See Sulfamethizole.

Sulfamethizole Tablets

Sulfamethizole Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_9H_{10}N_4O_2S_2$.

Identification—Triturate a quantity of finely powdered Sulfamethizole Tablets, equivalent to about 500 mg. of sulfamethizole, with 5 ml. of chloroform, and transfer it to a small filter. Wash with another 5-ml. portion of chloroform, and discard the filtrate. Triturate the residue with 10 ml. of ammonia T.S. for 5 minutes, add 10 ml. of water, and filter. Warm the filtrate until most of the ammonia is expelled, cool, and add acetic acid until the mixture is distinctly acid: a precipitate of sulfamethizole is formed. Collect the precipitate on a filter, wash it well with cold water, and dry at 105° for 1 hour: the sulfamethizole so obtained melts between 209° and 212°, page 814, and responds to the *Identification tests* under *Sulfamethizole,* page 674.

Disintegration, page 878—The disintegration time limit for Sulfamethizole Tablets is 30 minutes.

Weight variation, page 901—Sulfamethizole Tablets meet the requirements of the weight variation test for tablets.

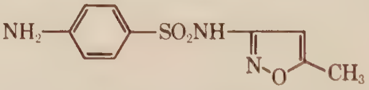
Assay—Weigh and finely powder not less than 20 Sulfamethizole Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg. of sulfamethizole, transfer it to a beaker or casserole, and proceed as directed in the *Assay* under *Sulfamethizole,* page 674, beginning with "Add 50 ml. of water and 20 ml. of hydrochloric acid . . . ."

Packaging and storage—Preserve Sulfamethizole Tablets in well-closed containers.

Tablets available—Sulfamethizole Tablets usually available contain the following amount of sulfamethizole: 250 mg.

Category and Dose—See Sulfamethizole.

Sulfamethoxazole*



N^1-(5-Methyl-3-isoxazolyl)sulfanilamide

$C_{10}H_{11}N_3O_3S$ Mol. wt. 253.28

Sulfamethoxazole, dried at 105° for 4 hours, contains not less than 98.5 percent and not more than 101.0 percent of $C_{10}H_{11}N_3O_3S$.

Description—Sulfamethoxazole occurs as a white to off-white, practically odorless, crystalline powder.

Solubility—Sulfamethoxazole is practically insoluble in water, in ether, and in chloroform. It is sparingly soluble in alcohol and is freely soluble in acetone and in dilute solutions of sodium hydroxide.

Identification—Dissolve about 100 mg. of Sulfamethoxazole in 2 ml. of hydrochloric acid, and add 3 ml. of sodium nitrite solution (1 in 100) and 1 ml. of sodium hydroxide solution (1 in 10) containing 10 mg. of betanaphthol: a red-orange precipitate is produced.

Melting range, page 814—Sulfamethoxazole melts between 170° and 173°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Sulfamethoxazole, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Sulfamethoxazole Reference Standard, similarly measured.

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* Patented. See notice, page ii.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Sulfamethoxazole in 0.1 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Sulfamethoxazole Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 257 mμ, do not differ by more than 2 percent.

Loss on drying, page 814—Dry Sulfamethoxazole at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Sulfamethoxazole yields not more than 0.1 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 200 mg. of Sulfamethoxazole meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Sulfanilamide and sulfanilic acid—

Standard preparation—Dissolve 100.0 mg. of NF Sulfamethoxazole Reference Standard in 0.1 ml. of stronger ammonia water, dilute to 10.0 ml. with methanol, and mix.

Reference preparation—Dissolve 20.0 mg. of USP Sulfanilamide Reference Standard and 20.0 mg. of sulfanilic acid in 10 ml. of stronger ammonia water, and dilute to 100.0 ml. with methanol. Pipet 2.0 ml. of the solution into a 50-ml. volumetric flask, add 10 ml. of stronger ammonia water, dilute to volume with methanol, and mix.

Test preparation—Dissolve 100.0 mg. of Sulfamethoxazole in 0.1 ml. of stronger ammonia water, dilute to 10.0 ml. with methanol, and mix.

Procedure—Perform thin-layer chromatography (see page 791), using silica gel G as the adsorbent and a solvent mixture of alcohol, *n*-heptane, chloroform, and glacial acetic acid (25:25:25:7). Spot 10 μl. of the *Standard preparation,* 25 μl. of the *Reference preparation,* and 10 μl. of the *Test preparation,* concurrently, at the starting line, and allow the solvent to ascend about 12 cm. Remove the plate from the chamber, and allow it to air-dry. Spray the plate with a solution prepared by dissolving 100 mg. of *p*-dimethylaminobenzaldehyde in 1 ml. of hydrochloric acid and diluting to 100 ml. with alcohol. Sulfamethoxazole produces a spot at about R_f 0.7, sulfanilamide appears at about R_f 0.5, and sulfanilic acid at about R_f 0.1. Any spots produced by sulfanilamide or sulfanilic acid from the *Test preparation* do not exceed in size or intensity similar spots, occurring at the respective R_f values, produced by sulfanilamide or sulfanilic acid from the *Reference preparation.*

Assay—Dissolve about 500 mg. of Sulfamethoxazole, previously dried at 105° for 4 hours and accurately weighed, in a mixture of 20 ml. of glacial acetic acid and 40 ml. of water, and add 15 ml. of hydrochloric acid. Cool to 15°, and titrate immediately with 0.1 *M* sodium nitrite, determining the end-point electrometrically using calomel and platinum electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 25.33 mg. of $C_{10}H_{11}N_3O_3S$.

Packaging and storage—Preserve Sulfamethoxazole in well-closed, light-resistant containers.

CATEGORY—Antibacterial.

USUAL DOSE RANGE—Initial **2 g.,** then **1 g.** two to three times a day.

Sulfamethoxazole Oral Suspension

Sulfamethoxazole Oral Suspension contains not less than 95.0 percent and not more than 110.0 percent of the labeled amount of $C_{10}H_{11}N_3O_3S$.

Identification—

A: Place a quantity of Sulfamethoxazole Oral Suspension, equivalent to about 100 mg. of sulfamethoxazole, in a 50-ml. centrifuge tube, add 5 ml. of stronger ammonia water, and shake gently. Add 25 ml. of methanol, shake thoroughly for 3 minutes, centrifuge, and decant the supernatant liquid into a 50-ml. volumetric flask, add methanol to volume, and mix. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 50 μl. of this solution and 50 μl. of a solution prepared by dissolving 100.0 mg. of NF Sulfamethoxazole Reference Standard in 5 ml. of stronger ammonia water and diluting to 50.0 ml. with methanol. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of alcohol, *n*-heptane, chloroform, and glacial acetic acid (25:25:25:7) until the solvent front has moved about 12 cm. from the origin. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with a solution prepared by dissolving 100 mg. of *p*-dimethylaminobenzaldehyde in 1 ml. of hydrochloric acid and diluting to 100 ml. with alcohol: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

B: Transfer a quantity of Sulfamethoxazole Oral Suspension, equivalent to about 500 mg. of sulfamethoxazole, to a 50-ml. centrifuge tube, add about 25 ml. of water, mix thoroughly, and centrifuge. Decant and discard the supernatant liquid, resuspend the residue in 25 ml. of water, mix thoroughly, and centrifuge again. Decant and discard the clear, supernatant liquid. Repeat the washing procedure an additional two times. Dissolve the residue in 10 ml. of hydrochloric acid, and add 15 ml. of sodium nitrite solution (1 in 100) and 5 ml. of sodium hydroxide solution (1 in 10) containing 10 mg. of betanaphthol: a red-orange precipitate is produced.

Assay—Mix an accurately measured volume of Sulfamethoxazole Oral Suspension, equivalent to about 1 g. of sulfamethoxazole, with 20 ml. of glacial acetic acid and 40 ml. of water, and add 15 ml. of hydrochloric acid. Cool to 15°, and titrate immediately with 0.1 *M* sodium nitrite, determining the end-point electrometrically using calomel and platinum electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 25.33 mg. of $C_{10}H_{11}N_3O_3S$.

Packaging and storage—Preserve Sulfamethoxazole Oral Suspension in tight, light-resistant containers.

Suspension available—Sulfamethoxazole Oral Suspension usually available contains the following amount of sulfamethoxazole: 500 mg. in 5 ml.

CATEGORY and DOSE—See Sulfamethoxazole.

Sulfamethoxazole Tablets

Sulfamethoxazole Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{10}H_{11}N_3O_3S$.

Identification—

A: Place a quantity of finely powdered Sulfamethoxazole Tablets, equivalent to about 100 mg. of sulfamethoxazole, in a 50-ml. centrifuge tube, add 5 ml. of stronger ammonia water, and shake gently. Add 25 ml. of methanol, shake thoroughly for 3 minutes, centrifuge, decant the supernatant liquid into a 50-ml. volumetric flask, add methanol to volume, and mix. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 50 μl. of this solution and 50 μl. of a solution prepared by dissolving 100.0 mg. of NF Sulfamethoxazole Reference Standard in 5 ml. of stronger ammonia water and diluting to 50.0 ml. with methanol. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of alcohol, *n*-heptane, chloroform, and glacial acetic acid (25:25:25:7) until the solvent front has moved about 12 cm. from the origin. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with a solution prepared by dissolving 100 mg. of *p*-dimethylaminobenzaldehyde in 1 ml. of hydrochloric acid and diluting to 100 ml. with alcohol: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

B: To a portion of finely powdered Sulfamethoxazole Tablets, equivalent to about 100 mg. of sulfamethoxazole, add 2 ml. of hydrochloric acid, 3 ml. of sodium nitrite solution (1 in 100), and 1 ml. of sodium hydroxide solution (1 in 10) containing 10 mg. of betanaphthol: a red-orange precipitate is formed.

Dissolution, Method I, page 802—Not less than 50 percent of the labeled amount of $C_{10}H_{11}N_3O_3S$ in Sulfamethoxazole Tablets dissolves into solution within 20 minutes, using a stirring speed of 100 r.p.m. and hydrochloric acid solution (7 in 100) as the *Dissolution Fluid*. Determine the amount of $C_{10}H_{11}N_3O_3S$ in solution by determining the ultraviolet absorbance of clear aliquots removed from the dissolution solution, at 265 mμ, in 1-cm. cells, with a suitable spectrophotometer, using hydrochloric acid solution (7 in 100) as the blank and utilizing a standard curve, representing absorbance *versus* concentration of NF Sulfamethoxazole Reference Standard.

Weight variation, page 901—Sulfamethoxazole Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Sulfamethoxazole Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg. of sulfamethoxazole, and dissolve in a mixture of 20 ml. of glacial acetic acid and 40 ml. of water, and add 15 ml. of hydrochloric acid. Cool to 15°, and titrate immediately with 0.1 *M* sodium nitrite, determining the end-point electrometrically using calomel and platinum electrodes. Each ml. of 0.1 *M* sodium nitrite is equivalent to 25.33 mg. of $C_{10}H_{11}N_3O_3S$.

Packaging and storage—Preserve Sulfamethoxazole Tablets in well-closed, light-resistant containers.

Tablets available—Sulfamethoxazole Tablets usually available contain the following amount of sulfamethoxazole: 500 mg.

CATEGORY and DOSE—See Sulfamethoxazole.

Sulfisoxazole and Phenazopyridine Hydrochloride Tablets

Sulfisoxazole and Phenazopyridine Hydrochloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{11}H_{13}N_3O_3S$ (sulfisoxazole), and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{11}N_5.HCl$ (phenazopyridine hydrochloride).

Identification—

A: Dissolve a portion of finely ground Sulfisoxazole and Phenazopyridine Hydrochloride Tablets, equivalent to about 10 mg. of sulfisoxazole, in 3 ml. of diluted hydrochloric acid, warming if necessary. Cool, add 3 drops of sodium nitrite solution (1 in 100), add water to make about 5 ml., and add 1 ml. of sodium hydroxide solution (1 in 10) containing 10 mg. of betanaphthol: a red-orange precipitate is formed.

B: Shake a quantity of finely powdered Sulfisoxazole and Phenazopyridine Hydrochloride Tablets, equivalent to about 10 mg. of phenazopyridine hydrochloride, with 15 ml. of hot water, and filter. To 5 ml. of the filtrate add 3 ml. of trinitrophenol T.S.: a yellow precipitate is formed.

Disintegration, page 878—The disintegration time limit for Sulfisoxazole and Phenazopyridine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Sulfisoxazole and Phenazopyridine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets when tested with respect to phenazopyridine hydrochloride content by the following special procedure: Place one tablet in an appropriate container, and add 5 ml. of 0.1 N sulfuric acid. Allow to stand about 25 minutes for the tablet to disintegrate, and then dilute quantitatively and stepwise with 0.1 N alcoholic sulfuric acid, filtering prior to final dilution, to provide a solution containing approximately 5 mcg. of phenazopyridine hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Phenazopyridine Hydrochloride Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 390 mμ, with a suitable spectrophotometer, using 0.1 N alcoholic sulfuric acid as the blank. Calculate the quantity, in mg., of $C_{11}H_{11}N_5.HCl$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity of phenazopyridine hydrochloride, in mg., in the tablet; D is the exact concentration, in mcg. per ml., of phenazopyridine hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration of the Reference Standard solution, in mcg. per ml.; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay for phenazopyridine hydrochloride—Weigh and finely powder not less than 10 Sulfisoxazole and Phenazopyridine Hydrochloride Tablets. Weigh accurately a portion of the powder, equivalent to about 5 mg. of phenazopyridine hydrochloride, and transfer to a glass-stoppered centrifuge tube. Add 25.0 ml. of a mixture of water and acetone (4:1), shake to dissolve completely, and then centrifuge. Transfer 15.0 ml. of the supernatant liquid to a 75-ml. coulometric cell, and add 1.0 ml. of diluted hydrochloric acid and a sufficient quantity of triple-distilled mercury to provide a suitable pool electrode. Immerse a saturated calomel reference electrode and a working platinum electrode into the sample solution, using appropriate salt bridges, and deaerate by bubbling nitrogen through the solution for approximately 10 minutes. Using a suitable controlled-potential coulometric titrator (see page 800) reduce the sample at -0.40 volt, with continued deaeration, until the observed cell current drops to 1/1000 of the initial current. Perform a blank determination, and make any necessary correction. Each coulomb of electricity is equivalent to 646.9 mcg. of $C_{11}H_{11}N_5.HCl$.

Assay for sulfisoxazole—

Standard preparation—Transfer about 500 mg. of USP Sulfisoxazole Reference Standard, previously dried at 105° for 2 hours and accurately weighed, to a 1000-ml. volumetric flask, dissolve in 50 ml. of 0.1 N sodium hydroxide, warming gently if necessary, and cool to room temperature. Add 200 ml. of 4 N sulfuric acid, cool to room temperature, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a second 1000-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Weigh and finely powder not less than 20 Sulfisoxazole and Phenazopyridine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg. of sulfisoxazole, to a 1000-ml. volumetric flask, add 20 ml. of sodium hydroxide solution (1 in 10), and dissolve the sample completely, heating if necessary. Cool to room temperature, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a 1000-ml. volumetric flask, add 20 ml. of diluted sulfuric acid, dilute to volume with water, and mix.

Procedure—Transfer 10.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of water (to serve as the blank) into separate 25-ml. volumetric flasks, and treat each flask as follows: Add 1.0 ml. of 4 *N* sulfuric acid, 1.0 ml. of sodium nitrite solution (1 in 1000), mix, and allow to stand for 5 minutes. Add 1.0 ml. of ammonium sulfamate solution (1 in 200), mix, and allow to stand for 2 minutes. Add 1.0 ml. of *N*-(1-naphthyl)ethylenediamine dihydrochloride solution (1 in 1000), dilute to volume with water, mix, and allow to stand for 15 minutes. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 540 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{11}H_{13}N_3O_3S$ in the portion of the Tablets taken by the formula $100C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Sulfisoxazole and Phenazopyridine Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Sulfisoxazole and Phenazopyridine Hydrochloride Tablets usually available contain the following amount of sulfisoxazole: 500 mg.; and of phenazopyridine hydrochloride: 50 mg.

CATEGORY—Antibacterial; urinary analgesic.

USUAL DOSE OF SULFISOXAZOLE—**1 g.** four times a day; OF PHENAZOPYRIDINE HYDROCHLORIDE—**100 mg.** four times a day.

Sublimed Sulfur

S At. wt. 32.06

Sublimed Sulfur, dried over phosphorus pentoxide for 4 hours, contains not less than 99.5 percent and not more than 100.5 percent of S.

Description—Sublimed Sulfur occurs as a fine, yellow, crystalline powder having a faint odor and taste.

Solubility—Sublimed Sulfur is practically insoluble in water, and nearly insoluble in alcohol. It is sparingly soluble in olive oil.

Solubility in carbon disulfide—One g. of Sublimed Sulfur dissolves slowly and usually incompletely in about 2 ml. of carbon disulfide.

Identification—Sublimed Sulfur burns in the air to sulfur dioxide, which can be recognized by its characteristic odor.

Residue on ignition, page 858—Sublimed Sulfur yields not more than 0.5 percent of residue on ignition.

Arsenic—Digest 2.5 g. of Sublimed Sulfur for 3 hours with 20 ml. of ammonia T.S., filter, and evaporate the clear filtrate to dryness on a steam bath. Add 15 ml. of diluted sulfuric acid and 1 ml. of 30 percent hydrogen peroxide solution, evaporate to strong fumes of sulfur trioxide, cool, add cautiously 10 ml. of water, and again evaporate to strong fumes, repeating if necessary to remove any trace of hydrogen peroxide. Cool, and dilute cautiously with water to 35 ml. This *Test Preparation* meets the requirements of the *Arsenic Test*, page 777 (4 parts per million As).

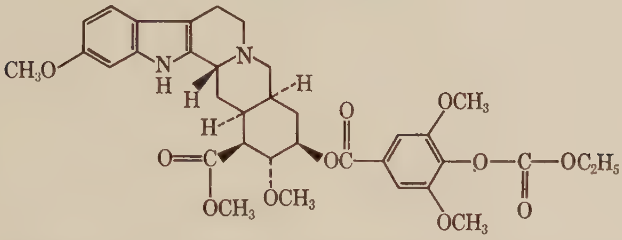
Assay—Proceed as directed under *Oxygen Flask Combustion*, page 823, using about 30 mg. of Sublimed Sulfur, previously dried over phosphorus pentoxide for 4 hours and accurately weighed, as the sample, and a mixture of 5 ml. of water and 2.5 ml. of hydrogen peroxide T.S. as the absorbing liquid. When the combustion is complete, fill the lip of the flask with water, loosen the stopper, then rinse the stopper, sample holder, and sides of the flask with water, and remove the stopper assembly. Heat the contents of the flask to boiling and boil for about 2 minutes. Cool to room temperature, add 3 drops of phenolphthalein T.S., and titrate with 0.05 *N* sodium hydroxide. Each ml. of 0.05 *N* sodium hydroxide is equivalent to 801.6 mcg. of S.

Packaging and storage—Preserve Sublimed Sulfur in well-closed containers.

CATEGORY—Parasiticide; scabicide.

Sulfurated Potash, page 569

Syrosingopine



Methyl 18β-Hydroxy-11,17α-dimethoxy-3β,20α-yohimban-16β-carboxylate 4-Hydroxy-3,5-dimethoxybenzoate Ethyl Carbonate (Ester)

$C_{35}H_{42}N_2O_{11}$ Mol. wt. 666.73

Syrosingopine, dried at 60° in vacuum for 3 hours, contains not less than 97.0 percent and not more than 101.0 percent of $C_{35}H_{42}N_2O_{11}$.

Description—Syrosingopine occurs as a white or slightly yellowish, crystalline, odorless powder. It is stable in air, but is affected by light.

Solubility—Syrosingopine is practically insoluble in water. It is slightly soluble in methanol and in ether and is freely soluble in chloroform and in acetic acid.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Syrosingopine, previously dried at 60° in vacuum for 3 hours, exhibits maxima only at the same wavelengths as that of NF Syrosingopine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 25,000 solution of Syrosingopine in methanol exhibits maxima and minima at the same wavelengths as that of NF Syrosingopine Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 258 mμ, do not differ by more than 3 percent.

Specific rotation, page 822—The specific rotation of Syrosingopine, previously dried at 60° in vacuum for 3 hours, determined in a solution in chloroform containing 100 mg. of Syrosingopine in each 10 ml., is not less than −93.0° and not more than −109.0°.

Loss on drying, page 814—Dry Syrosingopine at 60° in vacuum for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Syrosingopine yields not more than 0.1 percent of residue on ignition.

Assay—

Standard preparation—Dissolve about 50 mg. of NF Syrosingopine Reference Standard, previously dried at 60° in vacuum for 3 hours and accurately weighed, in sufficient chloroform to make 50.0 ml. Dilute 5.0 ml. of the solution to 50.0 ml. with chloroform. Prepare the solutions immediately before use and protect them from direct sunlight.

Assay preparation—Dissolve about 50 mg. of Syrosingopine, previously dried at 60° in vacuum for 3 hours and accurately weighed, in sufficient chloroform to make 50.0 ml. Dilute 5.0 ml. of the solution to 50.0 ml. with chloroform. Prepare the solutions immediately before use and protect them from direct sunlight.

Procedure—[Note: Carry out the entire procedure quickly, without exposure to direct sunlight. Perform the extractions in a suitable separator or in a suitably stoppered 50-ml. centrifuge tube, with separation being effected by centrifuging, the portion to be retained being withdrawn into a hypodermic syringe fitted with a 14-gauge, round-nose 15-cm. needle.]

Pipet 10.0 ml. each of the *Standard preparation* and the *Assay preparation* into separate extraction vessels. Add 10 ml. of citric acid solution (1 in 50), shake thoroughly for 2 minutes, then separate, and withdraw the chloroform. Wash the citric acid solution with two 10-ml. portions of chloroform, adding the washings to the main chloroform solution. To the combined chloroform solutions add 10 ml. of sodium bicarbonate solution (1 in 100), shake for 2 minutes, separate, and withdraw the chloroform, filtering it through a pledget of chloroform-washed cotton into a 50-ml. volumetric flask. Extract the aqueous layer in the extraction vessel with three 2-ml. portions of chloroform, passing each portion successively through the filter into the volumetric flask. Add methanol to volume, and mix. Pipet duplicate 5.0-ml. portions of each solution into 10-ml. volumetric flasks, and add 2.0 ml. of methanolic hydrochloric acid (1 in 10) to each flask. To one of the flasks containing the *Standard preparation* solution and to one containing the *Assay preparation* solution add 1.0 ml. of sodium nitrite solution (3 in 1000 in 50 percent methanol). To the second flask of each pair (constituting the blanks) add 1.0 ml. of 50 percent methanol. Mix, and allow to stand for 30 minutes. Add 0.5 ml. of ammonium sulfamate solution (1 in 20), dilute to volume with methanol, and allow to stand for 10 minutes. Concomitantly determine the absorbance of each solution in 1-cm. cells at the maximum at about 390 mμ, with a suitable spectrophotometer, using a mixture of methanol and chloroform (1 in 2) as the reference blank. Record the absorbance of the nitrite-treated solution from the *Standard preparation* as A_S, that of the nitrite-treated solution from the *Assay preparation* as A_U, that of the blank from the *Standard preparation* as $A°_S$, and that of the blank from the *Assay preparation* as $A°_U$. Calculate the quantity, in mg., of $C_{35}H_{42}N_2O_{11}$ in the portion of Syrosingopine taken by the formula $0.5C \times (A_U - A°_U)/(A_S - A°_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Syrosingopine in tight, light-resistant containers.

CATEGORY—Antihypertensive.

USUAL DOSE RANGE—Initial, **1 to 2 mg.** daily. Maintenance, **500 mcg. to 3 mg.** daily.

Syrosingopine Tablets

Syrosingopine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{35}H_{42}N_2O_{11}$.

Identification—Triturate an amount of powdered Syrosingopine Tablets, equivalent to about 2 mg. of syrosingopine, with 2 ml. of chloroform, and add sufficient methanol to make 50 ml. Shake the mixture vigorously for 5 minutes, and filter. Determine the ultraviolet absorption of the filtrate in a suitable spectrophotometer in the region of 258 mμ and 298 mμ against a blank composed of 2 ml. of chloroform diluted to 50 ml. with methanol. The ultraviolet absorption spectrum exhibits maxima and minima at the same wavelengths as that of NF Syrosingopine Reference Standard, similarly measured. A primary maximum is found at the wavelength of 258 ± 2 mμ and a secondary maximum at 298 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Syrosingopine Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Syrosingopine Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparation—Prepare as directed in the *Assay* under *Syrosingopine*, page 681.

Assay preparation—Weigh not less than 20 Syrosingopine Tablets and reduce them to a fine powder. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg. of syrosingopine, to a sintered-glass funnel of medium porosity. Add 10 ml. of chloroform and apply vacuum, collecting the chloroform extract in a 100-ml. volumetric flask. Repeat the extraction with eight additional 10-ml. portions of chloroform, dilute the combined extracts to volume with chloroform, and mix.

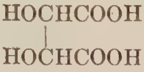
Procedure—Proceed as directed for *Procedure* in the *Assay* under *Syrosingopine*, page 681, beginning with "Pipet 10.0 ml. each of the *Standard preparation* and the *Assay preparation* into separate extraction vessels. . . ." Calculate the quantity, in mg., of $C_{35}H_{42}N_2O_{11}$ in the portion of the Tablets taken by the formula $0.1C \times (A_U - A°_U)/(A_S - A°_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Syrosingopine Tablets in tight, light-resistant containers.

Tablets available—Syrosingopine Tablets usually available contain the following amount of syrosingopine: 1 mg.

CATEGORY and DOSE—See Syrosingopine.

Tartaric Acid



$$\begin{array}{c}\mathrm{HOCHCOOH}\\ |\\ \mathrm{HOCHCOOH}\end{array}$$

$C_4H_6O_6$ Mol. wt. 150.09

Tartaric Acid, dried over phosphorus pentoxide for 3 hours, contains not less than 99.7 percent and not more than 100.5 percent of $C_4H_6O_6$.

Description—Tartaric Acid occurs as colorless or translucent crystals, or as a white, fine to granular, crystalline powder. It is odorless, has an acid taste, and is stable in air.

Solubility—Tartaric Acid is very soluble in water and is freely soluble in alcohol.

Identification—

A: Tartaric Acid responds to the tests for *Tartrate*, page 810.

B: Ignite Tartaric Acid: it gradually decomposes, emitting an odor resembling that of burning sugar (*distinction from citric acid*).

Loss on drying, page 814—Dry Tartaric Acid over phosphorus pentoxide for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Tartaric Acid yields not more than 0.05 percent of residue on ignition.

Oxalate—Nearly neutralize 10 ml. of a solution of Tartaric Acid (1 in 10) with ammonia T.S., and add 10 ml. of calcium sulfate T.S.: no turbidity is produced.

Sulfate—To 10 ml. of a solution of Tartaric Acid (1 in 100) add 3 drops of hydrochloric acid and 1 ml. of barium chloride T.S.: no turbidity is produced.

Heavy metals, *Method II*, page 806—The heavy metals limit for Tartaric Acid is 10 parts per million.

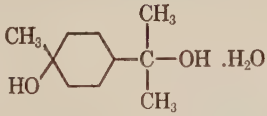
Assay—Place about 2 g. of Tartaric Acid, previously dried over phosphorus pentoxide for 3 hours and accurately weighed, in a conical flask. Dissolve it in 40 ml. of water, add a few drops of phenolphthalein T.S., and titrate with 1 *N* sodium hydroxide. Each ml. of 1 *N* sodium hydroxide is equivalent to 75.04 mg. of $C_4H_6O_6$.

Packaging and storage—Preserve Tartaric Acid in well-closed containers.

CATEGORY—Buffer.

Tartrate, Potassium Sodium, page 577

Terpin Hydrate



cis-p-Menthane-1,8-diol Hydrate

$C_{10}H_{20}O_2 . H_2O$ Mol. wt. 190.29

Terpin Hydrate contains not less than 98.0 percent and not more than 100.5 percent of $C_{10}H_{20}O_2$, calculated on the anhydrous basis.

Description—Terpin Hydrate occurs as colorless, lustrous crystals, or as a white powder. It has a slight odor, and effloresces in dry air. A hot solution of Terpin Hydrate (1 in 100) is neutral to litmus. When dried in vacuum at 60° for 2 hours, it melts at about 103°.

Solubility—Terpin Hydrate is slightly soluble in water, in chloroform, and in ether. It is soluble in alcohol, very soluble in boiling alcohol, and sparingly soluble in boiling water.

Identification—Add a few drops of sulfuric acid to a hot solution of Terpin Hydrate: the liquid becomes turbid and develops a strongly aromatic odor.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Terpin Hydrate, previously dried over a suitable desiccant for 4 hours, exhibits maxima only at the same wavelengths as that of NF Terpin Hydrate Reference Standard, similarly measured.

Water, page 900—Determine the water content of Terpin Hydrate by the titrimetric method: not less than 9.0 percent and not more than 10.0 percent is found.

Residue on ignition, page 858—Terpin Hydrate yields not more than 0.1 percent of residue on ignition.

Residual turpentine—Terpin Hydrate has no odor of turpentine oil.

Assay—

Internal standard solution—Dissolve about 1 g. of dodecyl alcohol, accurately weighed, in sufficient dehydrated alcohol to make 100.0 ml.

Standard preparation—Transfer about 40 mg. of NF Terpin Hydrate Reference Standard, accurately weighed, to a 10-ml. volumetric flask, and dissolve in about 6 ml. of dehydrated alcohol. Add 2.0 ml. of *Internal standard solution*, dilute to volume with dehydrated alcohol, and mix.

Assay preparation—Transfer about 200 mg. of Terpin Hydrate, accurately weighed, to a 50-ml. volumetric flask, and dissolve in about 30 ml. of dehydrated alcohol. Add 10.0 ml. of *Internal standard solution*, dilute to volume with dehydrated alcohol, and mix.

Calibration—Inject a suitable sized portion of the *Standard preparation* into a suitable gas chromatograph (see page 787) equipped with a flame-ionization detector. Under typical conditions, the instrument contains a 1.8-meter by 3-mm. stainless steel column packed with 10 percent polyethylene glycol 20,000 on 60 to 80-mesh silanized chromatographic siliceous earth. The column is maintained at 170°; the injection port and the detector are maintained at 170°; and helium is used as the carrier gas at a flow rate of 40 ml. per minute. In the detector, hydrogen is introduced at a rate of 44 ml. per minute, and air at a rate of 360 ml. per minute.

Measure the heights of the first (dodecyl alcohol) and second (terpin hydrate) peaks, and record the values as P_1 and P_2, respectively. Calculate the relative response factor, F, of equal weights of dodecyl alcohol and NF Terpin Hydrate Reference Standard, by the formula $(P_1/P_2) \times (W_2/W_1)$, in which W_2 represents the weight percent of NF Terpin Hydrate Reference Standard in the *Standard preparation*, calculated on the anhydrous basis, and W_1 represents the weight percent of dodecyl alcohol in the *Standard preparation*.

Procedure—Inject a suitable sized portion of the *Assay preparation* into the chromatograph, and obtain a chromatogram under the conditions described for *Calibration*. Measure the heights of the first (dodecyl alcohol) and second (terpin hydrate) peaks, and record the values as p_1 and p_2, respectively. Calculate the weight, in mg., of $C_{10}H_{20}O_2$ in the Terpin Hydrate taken by the formula $10 \times (p_2/p_1) \times C \times F$, in which C is the exact concentration, in mg. per ml., of the *Internal standard solution*, and F is as defined under *Calibration*.

Packaging and storage—Preserve Terpin Hydrate in tight containers.

CATEGORY—Expectorant.

USUAL DOSE RANGE—**125** to **300 mg.** every 6 hours.

Terpin Hydrate Elixir

Terpin Hydrate Elixir contains, in each 100 ml., not less than 1.53 g. and not more than 1.87 g. of $C_{10}H_{20}O_2 . H_2O$. It may be prepared as follows:

Terpin Hydrate	**17**	**g.**
Sweet Orange Peel Tincture	**20**	**ml.**
Benzaldehyde	**0.05**	**ml.**
Glycerin	**400**	**ml.**
Alcohol	**430**	**ml.**
Syrup	**100**	**ml.**
Purified Water, a sufficient quantity,		
To make	**1000**	**ml.**

Dissolve the terpin hydrate in the alcohol; add successively the tincture, the benzaldehyde, the glycerin, the syrup, and sufficient purified water to make the product measure 1000 ml.; mix well and filter if necessary, until the product is clear.

NOTE: The sweet orange peel tincture in the formula may be replaced by 1 ml. of orange oil dissolved in 15 ml. of alcohol.

Assay—

Internal standard solution—Dissolve about 1 g. of dodecyl alcohol, accurately weighed, in sufficient dehydrated alcohol to make 100.0 ml.

Standard preparation—Transfer about 34 mg. of NF Terpin Hydrate Reference Standard, accurately weighed, to a 10-ml. volumetric flask, and dissolve in about 6 ml. of dehydrated alcohol. Add 2.0 ml. of *Internal standard solution*, dilute to volume with dehydrated alcohol, and mix.

Assay preparation—Transfer an accurately measured volume of Terpin Hydrate Elixir, equivalent to about 170 mg. of terpin hydrate, to a separator, add 25 ml. of a saturated solution of sodium acetate, and shake for 1 minute. Allow to stand for 30 minutes with occasional shaking, and then extract with four 25-ml. portions of chloroform, filtering each extract through chloroform-moistened cotton into a beaker. Evaporate the combined extracts to a volume of about 12 ml. by warming on a steam bath and with the aid of a current of air, and then complete the evaporation to dryness without heating. Dissolve the residue in 15 ml. of dehydrated alcohol, and transfer the solution to a 50-ml. volumetric flask containing 10.0 ml. of *Internal standard solution.* Wash the beaker with sufficient dehydrated alcohol to bring to volume, and mix.

Calibration—Proceed as directed in the *Assay* under *Terpin Hydrate,* page 683, and calculate the response factor *F*.

Procedure—Inject a 0.5-μl. portion of the *Assay preparation* into a suitable gas chromatograph as described under *Calibration* in the *Assay* for *Terpin Hydrate,* page 683. Measure the heights of the dodecyl alcohol and terpin hydrate peaks, and record the values as p_1 and p_2, respectively. Calculate the quantity, in mg., of $C_{10}H_{20}O_2 . H_2O$ in each ml. of the Elixir taken by the formula $10 \times (p_2/p_1) \times (C/V) \times F \times 1.104$, in which C is the exact concentration, in mg. per ml., of the *Internal standard solution,* V is the volume, in ml., of the Elixir taken, F is the response factor as described under *Calibration,* and 1.104 is the factor converting anhydrous terpin ($C_{10}H_{20}O_2$) to terpin hydrate ($C_{10}H_{20}O_2 . H_2O$).

Alcohol content, page 772—Terpin Hydrate Elixir contains from 39 to 44 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Terpin Hydrate Elixir in tight containers.

CATEGORY—See Terpin Hydrate.
USUAL DOSE—**5 ml.**

One usual dose contains 85 mg. of Terpin Hydrate.

Terpin Hydrate and Codeine Elixir

Terpin Hydrate and Codeine Elixir contains, in each 100 ml., not less than 1.53 g. and not more than 1.87 g. of $C_{10}H_{20}O_2 . H_2O$ (terpin hydrate), and not less than 180 mg. and not more than 220 mg. of $C_{18}H_{21}NO_3 . H_2O$ (codeine). It may be prepared as follows:

Codeine	**2 g.**
Terpin Hydrate Elixir, a sufficient quantity,	
To make	**1000 ml.**

Dissolve the codeine in a sufficient quantity of the terpin hydrate elixir to make the product measure 1000 ml.

Identification—Transfer 1 ml. of Terpin Hydrate and Codeine Elixir to a 125-ml. separator containing 10 ml. of 0.1 *N* hydrochloric acid, extract with two 20-ml. portions of chloroform, and discard the chloroform extracts. Add 3 ml. of sodium hydroxide solution (1 in 10), extract with 20 ml. of chloroform, filter the chloroform extract through anhydrous sodium sulfate into a porcelain dish, and evaporate to dryness on a steam bath. To the residue add 1 ml. of sulfuric acid containing 2 drops of formaldehyde T.S.: an intense violet-blue color is produced (*presence of codeine*).

Assay for terpin hydrate—

Internal standard solution—Dissolve about 1 g. of dodecyl alcohol, accurately weighed, in sufficient dehydrated alcohol to make 100.0 ml.

Standard preparation—Transfer about 34 mg. of NF Terpin Hydrate Reference Standard, accurately weighed, to a 10-ml. volumetric flask, and dissolve in about 6 ml. of dehydrated alcohol. Add 2.0 ml. of *Internal standard solution,* dilute to volume with dehydrated alcohol, and mix.

Assay preparation—Transfer an accurately measured volume of Terpin Hydrate and Codeine Elixir, equivalent to about 170 mg. of terpin hydrate, to a separator. add 25 ml. of a saturated solution of sodium acetate, and shake for 1 minute. Allow to stand for 30 minutes with occasional shaking, and then extract with four 25-ml. portions of chloroform, filtering each extract through chloroform-moistened cotton into a beaker. Evaporate the combined extracts to a volume of about 12 ml. by warming on a steam bath and with the aid of a current of air, and then complete the evaporation to dryness without heating. Dissolve the residue in 15 ml. of dehydrated alcohol, and transfer the solution to a 50-ml. volumetric flask containing 10.0 ml. of *Internal standard solution.* Wash the beaker with sufficient dehydrated alcohol to bring to volume, and mix.

Calibration—Proceed as directed in the *Assay* under *Terpin Hydrate,* page 683, and calculate the response factor *F*.

Procedure—Inject a 0.5-μl. portion of the *Assay preparation* into a suitable chromatograph as described under *Calibration* in the *Assay* for *Terpin Hydrate,* page 683. Measure the heights of the dodecyl alcohol and terpin hydrate peaks, and record the values as p_1 and p_2, respectively. Calculate the quantity, in mg., of $C_{10}H_{20}O_2 . H_2O$ in each ml. of the Elixir taken by the formula $10 \times (p_2/p_1) \times (C/V) \times F \times 1.104$, in which C is the exact concentration, in mg. per ml., of the *Internal standard solution,* V is the volume, in ml., of the Elixir taken, F is the response factor as described under *Calibration*, and 1.104 is the factor converting anhydrous terpin ($C_{10}H_{20}O_2$) to terpin hydrate ($C_{10}H_{20}O_2.H_2O$).

Assay for codeine—Transfer an accurately measured volume of Terpin Hydrate and Codeine Elixir, equivalent to about 30 mg. of codeine, to a 125-ml. separator containing 10 ml. of 0.1 *N* hydrochloric acid. Extract with two 20-ml. portions of chloroform, transferring the chloroform extracts to a second separator. Wash the combined extracts with 5 ml. of water, discard the chloroform and add the washing to the original aqueous solution. Add 3 ml. of sodium hydroxide solution (1 in 10), and completely extract the codeine with five 25-ml. portions of chloroform, filtering the extracts through anhydrous sodium sulfate into a 250-ml. conical flask. Add 3 drops of methanolic methyl red T.S. to the combined chloroform extracts, and titrate with 0.01 *N* perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* perchloric acid is equivalent to 3.174 mg. of $C_{18}H_{21}NO_3.H_2O$.

Alcohol content, page 772—Terpin Hydrate and Codeine Elixir contains from 39 to 44 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Terpin Hydrate and Codeine Elixir in tight containers.

Category—See Terpin Hydrate.
Usual dose—**5 ml.**

One usual dose contains 10 mg. of Codeine and 85 mg. of Terpin Hydrate.

Terpin Hydrate and Dextromethorphan Hydrobromide Elixir

Terpin Hydrate and Dextromethorphan Hydrobromide Elixir contains, in each 100 ml., not less than 1.53 g. and not more than 1.87 g. of $C_{10}H_{20}O_2.H_2O$ (terpin hydrate), and not less than 180 mg. and not more than 220 mg. of $C_{18}H_{25}NO.HBr.H_2O$ (dextromethorphan hydrobromide). It may be prepared as follows:

Dextromethorphan Hydrobromide	**2 g.**
Terpin Hydrate Elixir, a sufficient quantity,	
To make	**1000 ml.**

Dissolve the dextromethorphan hydrobromide in a sufficient quantity of the terpin hydrate elixir to make the product measure 1000 ml.

Identification—Transfer 1 ml. of Terpin Hydrate and Dextromethorphan Hydrobromide Elixir to a 125-ml. separator containing 20 ml. of a saturated solution of sodium sulfate, extract with a 20-ml. portion of chloroform, transfer the chloroform extract to a conical flask, and evaporate to dryness on a steam bath. Dissolve the residue in 1 ml. of diluted hydrochloric acid, add 20 ml. of water, mix, transfer the solution to a separator, add 4 ml. of ammonia T.S., and extract with a 20-ml. portion of solvent hexane. Wash the hexane layer with two 20-ml. portions of water, filter the washed hexane solution through anhydrous sodium sulfate, and evaporate to dryness on a steam bath. To the residue add 1 ml. of sulfuric acid containing 2 drops of formaldehyde T.S.: a green color is produced (*presence of dextromethorphan hydrobromide*).

Assay for terpin hydrate—

Internal standard solution—Dissolve about 1 g. of dodecyl alcohol, accurately weighed, in sufficient dehydrated alcohol to make 100.0 ml.

Standard preparation—Transfer about 34 mg. of NF Terpin Hydrate Reference Standard, accurately weighed, to a 10-ml. volumetric flask, and dissolve in about 6 ml. of dehydrated alcohol. Add 2.0 ml. of *Internal standard solution*, dilute to volume with dehydrated alcohol, and mix.

Assay preparation—Transfer an accurately measured volume of Terpin Hydrate and Dextromethorphan Hydrobromide Elixir, equivalent to about 170 mg. of terpin hydrate, to a separator, add 25 ml. of a saturated solution of sodium acetate, and shake for 1 minute. Allow to stand for 30 minutes with occasional shaking, and then extract with four 25-ml. portions of chloroform, filtering each extract through chloroform-moistened cotton into a beaker. Evaporate the combined extracts to a volume of about 12 ml. by warming on a steam bath and with the aid of a current of air, and then complete the evaporation to dryness without heating. Dissolve the residue in 15 ml. of dehydrated alcohol, and transfer the solution to a 50-ml. volumetric flask containing 10.0 ml. of *Internal standard solution*. Wash the beaker with sufficient dehydrated alcohol to bring to volume, and mix.

Calibration—Proceed as directed in the *Assay* under *Terpin Hydrate*, page 683, and calculate the response factor *F*.

Procedure—Inject a 0.5-µl. portion of

the *Assay preparation* into a suitable chromatograph as described under *Calibration* in the *Assay* for *Terpin Hydrate*, page 683. Measure the heights of the dodecyl alcohol and terpin hydrate peaks, and record the values as p_1 and p_2, respectively. Calculate the quantity, in mg., of $C_{10}H_{20}O_2 . H_2O$ in each ml. of the Elixir taken by the formula $10 \times (p_2/p_1) \times (C/V) \times F \times 1.104$, in which C is the exact concentration, in mg. per ml., of the *Internal standard solution*, V is the volume, in ml., of the Elixir taken, F is the response factor as described under *Calibration*, and 1.104 is the factor converting anhydrous terpin ($C_{10}H_{20}O_2$) to terpin hydrate ($C_{10}H_{20}O_2 . H_2O$).

Assay for dextromethorphan hydrobromide—

Standard preparation—Dissolve about 50 mg. of NF Dextromethorphan Hydrobromide Reference Standard, accurately weighed, in sufficient chloroform to make 100.0 ml. Dilute 10.0 ml. of this solution to 50.0 ml. with chloroform.

Assay preparation—Transfer a 10.0-ml. portion of Terpin Hydrate and Dextromethorphan Hydrobromide Elixir to a 125-ml. separator, add 5 ml. of 1 *N* hydrochloric acid, and extract the solution with four 25-ml. portions of solvent hexane. Wash each hexane extract with 5 ml. of water, adding the washings to the aqueous solution. Discard the washed hexane extracts. To the aqueous solution, add 10 ml. of 1 *N* sodium hydroxide, and allow to stand for 5 minutes. Extract with six 30-ml. portions of chloroform, collecting the extracts in a 200-ml. volumetric flask, dilute to volume with chloroform, and mix.

Procedure—Pipet into 3 individual separators 5.0 ml. of the *Standard preparation*, 5.0 ml. of the *Assay preparation*, and 5.0 ml. of chloroform to serve as the blank. To each separator add 25 ml. of pH 5.3 buffer solution (38 g. $NaH_2PO_4 . H_2O$ and 3.8 g. $Na_2HPO_4 . 7H_2O$ in sufficient water to make 1000 ml.), and 5 ml. of sodium bromocresol green solution (prepared by dissolving 100 mg. of bromocresol green in 1.4 ml. of 0.1 *N* sodium hydroxide and diluting to 100 ml. with pH 5.3 buffer solution). Extract the aqueous solutions in the separators with three 25-ml. portions of chloroform, combining the extracts in respective 100-ml. volumetric flasks. Dilute to volume with chloroform, and mix. Determine the absorbances of the chloroform solutions in 1-cm. cells, at the maximum at about 420 mμ, with a suitable spectrophotometer, against the blank. Calculate the quantity, in mg., of $C_{18}H_{25}NO . HBr . H_2O$ in each ml. of the Elixir by the formula $0.2 \times (C/V) \times (A_U/A_S)$, in which A_U is the absorbance of the solution from the *Assay preparation*, A_S is the absorbance of the solution from the *Standard preparation*, C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Elixir taken.

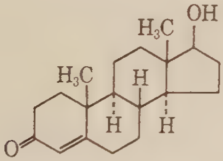
Alcohol content—Determine the alcohol content by the gas-liquid chromatographic procedure, page 772. Terpin Hydrate and Dextromethorphan Hydrobromide Elixir contains from 39 to 44 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Terpin Hydrate and Dextromethorphan Hydrobromide Elixir in tight containers.

CATEGORY—Expectorant; antitussive.
USUAL DOSE—**5 ml.**

One usual dose contains 10 mg. of Dextromethorphan Hydrobromide and 85 mg. of Terpin Hydrate.

Testosterone



17β-Hydroxyandrost-4-en-3-one

$C_{19}H_{28}O_2$ Mol. wt. 288.43

Testosterone contains not less than 97.0 percent and not more than 103.0 percent of $C_{19}H_{28}O_2$, calculated on the dried basis.

Description—Testosterone occurs as white or slightly creamy white crystals or crystalline powder. It is odorless and is stable in air.

Solubility—Testosterone is practically insoluble in water. It is freely soluble in dehydrated alcohol and in chloroform. It is slightly soluble in ether. It is soluble in dioxane and in vegetable oils.

Melting range, *Class Ia,* page 815—Testosterone melts between 153° and 157°.

Infrared absorption, page 866—The

infrared absorption spectrum of a potassium bromide dispersion of Testosterone, previously dried in vacuum over phosphorus pentoxide for 4 hours, exhibits maxima only at the same wavelengths as that of NF Testosterone Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Testosterone in methanol exhibits maxima and minima at the same wavelengths as that of NF Testosterone Reference Standard, similarly measured.

Specific rotation, page 822—The specific rotation of Testosterone, previously dried in vacuum over phosphorus pentoxide for 4 hours, determined in a solution in dioxane containing 100 mg. of Testosterone in each 10 ml., is between +101° and +105°.

Loss on drying, page 814—Dry Testosterone in vacuum over phosphorus pentoxide for 4 hours: it loses not more than 1 percent of its weight.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity,* page 876, using NF Testosterone Reference Standard.

Test preparation—Weigh accurately about 80 mg. of Testosterone previously dried in vacuum over phosphorus pentoxide for 4 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity,* page 876, using a solvent system consisting of benzene and ethyl acetate (1:1), and determining the absorbance at the maximum at about 241 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation,* and W is the weight, in mg., of Testosterone taken: not more than 3 percent is found.

Assay—Transfer about 50 mg. of Testosterone, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 5.0 ml. of the solution to a 250-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Testosterone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{19}H_{28}O_2$ in the Testosterone taken by the formula $5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Testosterone in well-closed containers.

CATEGORY—Androgen.

USUAL DOSE—Buccal, **10 mg.** daily. Implantation, **300 mg.** Intramuscular, **25 mg.** twice a week to once daily, depending on condition being treated.

Testosterone Pellets

Testosterone Pellets are sterile pellets composed of testosterone in compressed form, without the presence of any binder, diluent, or excipient. They contain not less than 97.0 percent and not more than 103.0 percent of $C_{19}H_{28}O_2$.

Melting range, Infrared absorption, Ultraviolet absorption, and Specific rotation—Testosterone Pellets meet the requirements for *Melting range, Infrared absorption, Ultraviolet absorption,* and *Specific rotation* under *Testosterone,* page 687.

Solubility in chloroform—A solution of 50 mg. of powdered Testosterone Pellets in 2 ml. of chloroform is clear and practically free from insoluble residue.

Weight variation—Weigh 5 Testosterone Pellets singly, and calculate the average weight. The average weight is not less than 95.0 percent and not more than 105.0 percent of the labeled weight of testosterone, and each pellet weighs not less than 90.0 percent and not more than 110.0 percent of the labeled weight of testosterone.

Sterility—Testosterone Pellets meet the requirements under *Sterility Tests,* page 874.

Assay—Weigh and finely powder not less than 10 Testosterone Pellets, and proceed as directed in the *Assay* under *Testosterone,* page 687, using about 50 mg. of the powder, accurately weighed, as the sample.

Packaging and storage—Preserve Testosterone Pellets in tight containers holding one Pellet each and suitable for maintaining sterile contents.

Pellets available—Testosterone Pellets usually available contain the following amount of testosterone: 75 mg.

CATEGORY and DOSE—See Testosterone.

Sterile Testosterone Suspension

Sterile Testosterone Suspension is a sterile suspension of testosterone in an aqueous medium. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{19}H_{28}O_2$.

Identification—

A: Testosterone obtained by filtration and washing, as in the *Assay*, and dried to constant weight at 105°, melts between 152° and 157°, page 814, and meets the requirements for *Infrared absorption* and *Ultraviolet absorption* under *Testosterone*, page 687.

B: The specific rotation (page 822) of testosterone, obtained and dried as in *Identification test A*, determined in a solution in dioxane containing 100 mg. of testosterone in each 10 ml., is not less than $+101°$ and not more than $+105°$.

pH, page 824—The pH of Sterile Testosterone Suspension is between 4.0 and 7.5.

Other requirements—Sterile Testosterone Suspension meets the requirements under *Injections*, page 810.

Assay—Shake well, and measure accurately, a volume of Sterile Testosterone Suspension, equivalent to about 100 mg. of testosterone, and filter it through a sintered-glass crucible, previously dried at 105°. If the filtrate is not clear, again filter it through the same crucible into the same receiver. Wash the residue in the filter with several 5-ml. portions of water until 2 ml. of the last washing, when evaporated on a steam bath, leaves a negligible residue. Dry the crucible and the collected testosterone at 105° for 1 hour. Completely dissolve the testosterone with several portions of methanol, collect the solution and washings in a 200-ml. volumetric flask, add methanol to volume, and mix. Pipet 5.0 ml. of this solution into a 250-ml. volumetric flask, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Testosterone Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 241 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{19}H_{28}O_2$, in each ml. of the Suspension taken by the formula $10 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., V is the volume, in ml., of the Suspension taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Sterile Testosterone Suspension in single-dose or in multiple-dose containers, preferably of Type I glass.

Suspensions available—Sterile Testosterone Suspension usually available contains the following amounts of testosterone: 250 and 500 mg. in 10 ml.

CATEGORY and DOSE—See Testosterone.

Tetanus and Gas Gangrene Antitoxins

Tetanus and Gas Gangrene Antitoxins is a sterile solution of antitoxic substances obtained from the blood of healthy animals which have been immunized against the toxins of *Clostridium tetani*, *Clostridium perfringens*, and *Clostridium septicum*. Each package of the Antitoxins contains not less than 1500 units of tetanus antitoxin and not less than 2000 units of each of the other component antitoxins. Tetanus and Gas Gangrene Antitoxins complies with the requirements of the United States Public Health Service.

Description—Tetanus and Gas Gangrene Antitoxins is a transparent or slightly opalescent liquid having a faint brownish, yellowish, or greenish color, nearly odorless or having an odor due to the presence of a preservative; it may have a slight granular deposit. It must be free from harmful substances detectable by animal inoculation and must not contain an excessive proportion of preservative (not more than 0.5 percent of phenol or 0.4 percent of cresol, if either of these is used).

Regulations—The potency of the Antitoxin is expressed in antitoxic units and the units are those of the Tetanus, Perfringens, and Vibrion Septique antitoxins prescribed by the United States Public Health Service.

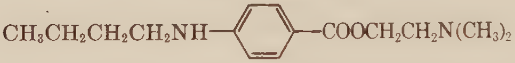
The outside label must indicate the minimum number of antitoxic units of each antitoxin in the package, the manufacturer's lot number of the Antitoxins, the name, address, and license number of the manufacturer, the genus of animal employed, and the date beyond which the minimum potency of the contents, as declared on the label, may not be maintained.

Preservation and storage—Preserve Tetanus and Gas Gangrene Antitoxins at a temperature between 2° and 8°, preferably at the lower limit. It must be dispensed in the unopened glass container in which it was placed by the manufacturer.

CATEGORY—Immunizing agent.

USUAL DOSE—Parenteral, prophylactic, the contents of one or more packages.

Tetracaine



2-(Dimethylamino)ethyl *p*-(Butylamino)benzoate

$C_{15}H_{24}N_2O_2$ Mol. wt. 264.37

Tetracaine contains not less than 98.0 percent and not more than 101.0 percent of $C_{15}H_{24}N_2O_2$, calculated on the dried basis.

Description—Tetracaine occurs as a white or light yellow, waxy solid.

Solubility—Tetracaine is very slightly soluble in water. It is soluble in alcohol, in ether, in benzene, and in chloroform.

Identification—Dissolve 100 mg. in 10 ml. of 0.1 *N* hydrochloric acid, add 1 ml. of potassium thiocyanate solution (1 in 4): a crystalline precipitate is formed. Recrystallize the precipitate from water, and dry at 80° for 2 hours: it melts between 130° and 132°, page 814.

Melting range, page 814—Tetracaine melts between 41° and 46°.

Ultraviolet absorption, page 866—Dissolve about 90 mg. of Tetracaine, accurately weighed, in 10 ml. of 0.1 *N* hydrochloric acid in a 500-ml. volumetric flask, dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, add 2 ml. of 10 percent pH 6.0 phosphate buffer solution (see page 783), dilute to volume with water, and mix. The ultraviolet absorption spectrum of this solution exhibits maxima and minima at the same wavelengths as that of a 1 in 100,000 solution of USP Tetracaine Hydrochloride Reference Standard in a solution of water and 10 percent pH 6.0 phosphate buffer, see page 783 (50:1), and the respective absorptivities, calculated on the dried basis and in terms of the base, at the point of maximum absorbance occurring at about 310 mμ, do not differ by more than 2 percent.

Loss on drying, page 814—Dry Tetracaine over phosphorus pentoxide in a vacuum desiccator for 18 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Tetracaine yields not more than 0.1 percent of residue on ignition.

Assay—Transfer about 500 mg. of Tetracaine, accurately weighed, to a suitable vessel. Add 5 ml. of hydrochloric acid and 50 ml. of water, cool to 15°, add about 25 g. of crushed ice, and slowly titrate with 0.1 *M* sodium nitrite, stirring vigorously, until a glass rod dipped into the titrated solution produces an immediate blue ring when touched to starch iodide paper. When the titration is complete, the end-point is reproducible after the mixture has been allowed to stand for 1 minute. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *M* sodium nitrite is equivalent to 26.44 mg. of $C_{15}H_{24}N_2O_2$.

Packaging and storage—Preserve Tetracaine in tight, light-resistant containers.

CATEGORY—Local anesthetic.

APPLICATION—Topically, as a 0.5 percent ointment to the conjunctiva.

Tetracaine Ophthalmic Ointment

Tetracaine Ophthalmic Ointment contains not less than 0.45 percent and not more than 0.55 percent of $C_{15}H_{24}N_2O_2$ in white petrolatum.

Identification—

A: The solution employed for measurement of absorbance in the *Assay* exhibits a maximum at 310 ± 2 mμ.

B: Dissolve 5 g. of Tetracaine Ophthalmic Ointment in 50 ml. of ether, extract the ether solution with 5 ml. of diluted hydrochloric acid, and filter the extract. To the extract add 2 ml. of potassium thiocyanate solution (1 in 2): a crystalline precipitate is formed, and when recrystallized from water and dried at 80° for 2 hours, it melts between 130° and 132°, page 814.

Metal particles—Tetracaine Ophthalmic Ointment meets the requirements of the test for *Metal Particles—Ophthalmic Ointments*, page 816.

Weight variation, page 901—Tetracaine Ophthalmic Ointment meets the requirements of the weight variation test for ointments.

Assay—

Standard preparation—Weigh accurately about 20 mg. of USP Tetracaine Hydrochloride Reference Standard, previously dried over phosphorus pentoxide in a vacuum desiccator for 18 hours, dissolve in sufficient water to make 100.0 ml., and mix. Pipet 5.0 ml. of this solution into a 100-ml. volumetric flask, add 5 ml. of 0.05 N hydrochloric acid and 10 ml. of 10 percent, pH 6.0 phosphate buffer (see page 783), dilute to volume with water, and mix.

Assay preparation—Weigh accurately a portion of Tetracaine Ophthalmic Ointment, equivalent to about 9 mg. of tetracaine, transfer to a separator, and dissolve in 15 ml. of ether. Extract with one 20-ml. portion and two 10-ml. portions of 0.05 N hydrochloric acid, collecting the extracts in a second separator, and make alkaline by the addition of 5 ml. of sodium carbonate T.S. Extract immediately with two 50-ml. portions of ether, collecting the extracts in a separator. Wash the ether extracts with 20 ml. of water, discarding the wash solution, and extract the ether solution with two 20-ml. portions and one 5-ml. portion of 0.05 N hydrochloric acid, collecting the extracts in a 50-ml. volumetric flask. Dilute to volume with water, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, add 10 ml. of 10 percent, pH 6.0 phosphate buffer (see page 783), dilute to volume with water, and mix.

Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 310 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{15}H_{24}N_2O_2$ in the portion of the Ointment taken by the formula $C \times 0.8788 \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of USP Tetracaine Hydrochloride Reference Standard in the *Standard preparation*, and 0.8788 is the ratio of the molecular weight of tetracaine to that of tetracaine hydrochloride.

Packaging and storage—Preserve Tetracaine Ophthalmic Ointment in collapsible ophthalmic ointment tubes.

CATEGORY and APPLICATION—See Tetracaine.

Tetracaine and Procaine Hydrochlorides and Levarterenol Bitartrate Injection, page 593
Tetracaine and Procaine Hydrochlorides and Levonordefrin Injection, page 594
Tetracaine, Procaine and Phenylephrine Hydrochlorides Injection, page 595

Tetracycline Hydrochloride for Ophthalmic Solution

Tetracycline Hydrochloride for Ophthalmic Solution is a sterile, dry mixture of tetracycline hydrochloride and one or more suitable buffers. It contains not less than 85.0 percent of the labeled amount of $C_{22}H_{24}N_2O_8 . HCl$. It may contain one or more suitable preservatives and diluents. Tetracycline Hydrochloride for Ophthalmic Solution conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Clarity of solution—Dissolve Tetracycline Hydrochloride for Ophthalmic Solution in the solvent and in the concentration recommended on the label: the solution is clear.

Packaging and storage—Preserve Tetracycline Hydrochloride for Ophthalmic Solution in well-closed containers.

Labeling—Label Tetracycline Hydrochloride for Ophthalmic Solution to indicate that the potency of the prepared solution, when stored at 15°, is maintained for 7 days. Tetracycline Hydrochloride for Ophthalmic Solution meets the requirements for *Labeling* under *Injections*, page 810.

Size available—Tetracycline Hydrochloride for Ophthalmic Solution usually available contains the following amount of tetracycline hydrochloride: 25 mg. in a 5-ml. container.

CATEGORY—Antibacterial.

USUAL DOSE OF TETRACYCLINE HYDROCHLORIDE FOR OPHTHALMIC SOLUTION—Topically, **0.1** to **0.2 ml.** of 0.5 percent solution applied to eyelid or conjunctiva.

Tetracycline Hydrochloride Tablets

Tetracycline Hydrochloride Tablets contain not less than 85.0 percent of the labeled amount of $C_{22}H_{24}N_2O_8.HCl$. Tetracycline Hydrochloride Tablets conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Tetracycline Hydrochloride Tablets in well-closed containers.

Tablets available—Tetracycline Hydrochloride Tablets usually available contain the following amounts of tetracycline hydrochloride: 50, 100, and 250 mg.

CATEGORY—Antibacterial.

USUAL DOSE RANGE OF TETRACYCLINE HYDROCHLORIDE—**250** to **500 mg.** four times a day.

Tetracycline Phosphate Complex*

Tetracycline Phosphate Complex has a potency of not less than 750.0 mcg. per mg., as tetracycline hydrochloride, on the anhydrous basis. Tetracycline Phosphate Complex conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Tetracycline Phosphate Complex occurs as a yellow, odorless, crystalline powder.

Solubility—Tetracycline Phosphate Complex is sparingly soluble in water, slightly soluble in methanol, and very slightly soluble in acetone.

Packaging and storage—Preserve Tetracycline Phosphate Complex in tight containers.

CATEGORY—Antibacterial.

USUAL DOSE—The equivalent of **250 mg.** of tetracycline hydrochloride four times a day.

USUAL DOSE RANGE—**250** to **500 mg.**

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* Patented. See notice, page ii.

Tetracycline Phosphate Complex Capsules

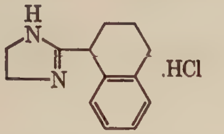
Tetracycline Phosphate Complex Capsules contain an amount of tetracycline phosphate complex equivalent to not less than 85.0 percent of the labeled amount of tetracycline hydrochloride ($C_{22}H_{24}N_2O_8.HCl$). Tetracycline Phosphate Complex Capsules conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Tetracycline Phosphate Complex Capsules in tight containers.

Capsules available—Tetracycline Phosphate Complex Capsules usually available contain the equivalent of the following amounts of tetracycline hydrochloride: 100, 250, and 500 mg.

CATEGORY and DOSE—See Tetracycline Phosphate Complex.

Tetrahydrozoline Hydrochloride*



2-(1,2,3,4-Tetrahydro-1-naphthyl)-2-imidazoline Monohydrochloride

$C_{13}H_{16}N_2.HCl$ Mol. wt. 236.75

Tetrahydrozoline Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{13}H_{16}N_2.HCl$, calculated on the dried basis.

Description—Tetrahydrozoline Hydrochloride occurs as a white, odorless solid.

Solubility—Tetrahydrozoline Hydrochloride is freely soluble in water and in alcohol. It is very slightly soluble in chloroform, and practically insoluble in ether.

Identification—A solution of Tetrahydrozoline Hydrochloride (1 in 200) responds to the test for *Chloride,* page 808.

Melting range, *Class Ia,* page 815—Tetrahydrozoline Hydrochloride melts between 253° and 259°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Tetrahydrozoline Hydrochloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Tetrahydrozoline Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2000 solution of Tetrahydrozoline Hydrochloride in water exhibits maxima and minima at the same wavelengths as that of NF Tetrahydrozoline Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the points of maximum absorbance occurring at about 264 mμ and 271 mμ, do not differ by more than 4 percent.

Loss on drying, page 814—Dry Tetrahydrozoline Hydrochloride at 105° for 2 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Tetrahydrozoline Hydrochloride yields not more than 0.1 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Tetrahydrozoline Hydrochloride in 23 ml. of water and add 2 ml. of diluted acetic acid: the heavy metals limit for Tetrahydrozoline Hydrochloride is 50 parts per million.

Assay—Transfer about 400 mg. of Tetrahydrozoline Hydrochloride, accurately weighed, to a 250-ml. tall-form beaker and dissolve it in 60 ml. of glacial acetic acid, heating if necessary. Add 5 ml. of acetic anhydride, 5 ml. of mercuric acetate T.S., and 1 drop of quinaldine red T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 23.68 mg. of $C_{13}H_{16}N_2.HCl$.

Packaging and storage—Preserve Tetrahydrozoline Hydrochloride in tight containers.

CATEGORY—Adrenergic (vasoconstrictor).

APPLICATION—Applied as a 0.05 or 0.1 percent solution as nasal drops or spray at 4-hour intervals. To the eye as a 0.05 percent solution.

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* Patented. See notice, page ii.

Tetrahydrozoline Hydrochloride Ophthalmic Solution*

Tetrahydrozoline Hydrochloride Ophthalmic Solution is a sterile solution of tetrahydrozoline hydrochloride in water. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{13}H_{16}N_2.HCl$.

Identification—The ultraviolet absorption spectrum of Tetrahydrozoline Hydrochloride Ophthalmic Solution, diluted with 0.1 *N* hydrochloric acid, if necessary, to provide a concentration of 1:2000, exhibits maxima and minima at the same wavelengths as that of NF Tetrahydrozoline Hydrochloride Reference Standard, similarly measured, page 856.

pH, page 824—The pH of Tetrahydrozoline Hydrochloride Ophthalmic Solution is between 6.2 and 6.5.

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* Patented. See notice, page ii.

Sterility—Tetrahydrozoline Hydrochloride Ophthalmic Solution meets the requirements under *Sterility Tests*, page 874.

Assay—

Standard preparation—Transfer about 50 mg. of NF Tetrahydrozoline Hydrochloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Transfer 2.0 ml. of the *Standard preparation* to a 50-ml. volumetric flask. Transfer an accurately measured volume of Tetrahydrozoline Hydrochloride Ophthalmic Solution, equivalent to about 1 mg. of tetrahydrozoline hydrochloride, to a second 50-ml. flask, and transfer 2 ml. of water to a third 50-ml. volumetric flask to serve as the blank. To each flask add 5.0 ml. of a solution of bromophenol blue sodium salt (1 in 1000), then dilute each flask to volume with 0.05 *N* potassium biphthalate, and mix. Allow to stand for 20 minutes, and filter each mixture through a suitable paper (such as Whatman No. 42 or equivalent) which does not absorb the dye, discarding the first 15 ml. of filtrate. Transfer 20.0 ml. of the subsequent filtrate to separate 125-ml. separators, and extract each solution with four 20-ml. portions of chloroform, filtering each extract through a pledget of glass wool into a 100-ml. volumetric flask. Dilute the combined extracts from each solution to volume with chloroform, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 415 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the sample solution as A_U. Calculate the quantity, in mcg., of $C_{13}H_{16}N_2 . HCl$ in each ml. of the Solution taken by the formula $2 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Solution taken.

Packaging and storage—Preserve Tetrahydrozoline Hydrochloride Ophthalmic Solution in tight containers.

Solution available—Tetrahydrozoline Hydrochloride Ophthalmic Solution usually available contains 0.05 percent of tetrahydrozoline hydrochloride.

CATEGORY and APPLICATION—See Tetrahydrozoline Hydrochloride.

Tetrahydrozoline Hydrochloride Solution

Tetrahydrozoline Hydrochloride Solution is a solution of tetrahydrozoline hydrochloride in water adjusted to a suitable tonicity. It may contain a preservative. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{13}H_{16}N_2 . HCl$.

Identification—The ultraviolet absorption spectrum of Tetrahydrozoline Hydrochloride Solution, suitably diluted with water, if necessary, to provide a concentration of about 1 in 2000, exhibits maxima and minima at the same wavelengths as that of NF Tetrahydrozoline Hydrochloride Reference Standard, similarly measured.

pH, page 824—The pH of Tetrahydrozoline Hydrochloride solution is between 5.3 and 6.5.

Assay—

Oxidized nitroprusside reagent—Dissolve 1.0 g. of sodium nitroferricyanide in sufficient water to make 10.0 ml. (*Solution A*). Dissolve 1.0 g. of potassium ferricyanide in sufficient water to make 10.0 ml. (*Solution B*). Transfer 1.0 ml. each of *Solution A* and of *Solution B* to a 100-ml. volumetric flask, add 1 ml. of sodium hydroxide solution (1 in 10), and allow to stand until the solution changes to a light yellow color (about 20 to 30 minutes). Dilute to volume with water, and mix. Store in a refrigerator or keep in an ice bath, and use within 4 hours.

Standard preparation—Weigh accurately about 20 mg. of NF Tetrahydrozoline Hydrochloride Reference Standard, and dissolve in sufficient water to make 200.0 ml.

Assay preparation—Transfer an accurately measured volume of Tetrahydrozoline Hydrochloride Solution, equivalent to about 10 mg. of tetrahydrozoline hydrochloride, to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate glass-stoppered test tubes. Prepare a blank consisting of 5.0 ml. of water in a third tube. To each tube add 4.0 ml. of *Oxidized nitroprusside reagent*, mix, and allow to stand for 15 minutes at 30°. Concomitantly determine the absorbances of the solutions in 1-cm. cells at the maximum at about 570 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{13}H_{16}N_2 . HCl$ in each ml. of the Solution taken by the formula $0.1 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration of the *Stan-*

dard preparation, in mcg. per ml., and V is the volume, in ml., of the Solution taken.

Packaging and storage—Preserve Tetrahydrozoline Hydrochloride Solution in tight containers.

Solutions available—Tetrahydrozoline Hydrochloride Solution usually available contains 0.05 and 0.1 percent of tetrahydrozoline hydrochloride.

CATEGORY and APPLICATION—See Tetrahydrozoline Hydrochloride.

Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets

Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of $C_7H_8N_4O_2.H_2O$ (theophylline), of $C_{10}H_{15}NO.HCl$ (ephedrine hydrochloride), and of $C_{12}H_{12}N_2O_3$ (phenobarbital).

Identification—The *Theophylline assay preparation*, prepared as directed in the *Assay*, exhibits an ultraviolet absorption maximum at 275 ± 2 mμ, the *Ephedrine hydrochloride assay preparation* at 257 ± 2 mμ, and the *Phenobarbital assay preparation* at 240 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets is 10 minutes.

Dissolution, *Method II*, page 802—Place one Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablet in each of the six tubes of the basket rack assembly, and operate the apparatus, using 750 ml. of simulated gastric fluid T.S. maintained at 37 ± 2° as the *Dissolution Fluid:* not less than 66 percent of the labeled amount of $C_7H_8N_4O_2.H_2O$ (theophylline) in the Tablets dissolves into solution within 2.0 minutes. Determine the amount of $C_7H_8N_4O_2.H_2O$ in solution by determining the ultraviolet absorbance of filtered aliquots removed from the dissolution solution, diluted with water to a concentration of about 8 mcg. of theophylline per ml., at the maximum at about 275 mμ, in 1-cm. cells, with a suitable spectrophotometer, using as the blank simulated gastric fluid T.S. diluted with water to the same degree as the sample solution, and utilizing a standard curve, representing absorbance *versus* concentration of USP Theophylline Reference Standard, similarly measured. Calculate the amount of theophylline dissolved per tablet.

Content uniformity, *Method I*, page 799—Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets meet the requirements of the content uniformity test for tablets when assayed for ephedrine hydrochloride and for phenobarbital content.

Assay—

Preparation of chromatographic columns—

Column A—Pack a pledget of fine glass wool in the base of a chromatographic tube (a 22 × 250-mm. test tube to which is fused a 5-cm. length of 6 or 8-mm. tubing) with the aid of a tamping rod at least 30 cm. long and having a disk with a diameter about 1 mm. less than that of the chromatographic tube. To 500 mg. of purified siliceous earth in a 100-ml. beaker add 0.3 ml. of 2 M tribasic sodium phosphate, and incorporate by kneading thoroughly to a uniform mixture. Transfer to the tube and pack lightly with the tamping rod.

Weigh and finely powder not less than 20 Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 9 mg. of ephedrine hydrochloride, to a 100-ml. beaker, add 2.0 ml. of 2 N tribasic sodium phosphate, and mix well. Add 3 g. of purified siliceous earth, mix thoroughly, and transfer to the column in three portions on top of the first tribasic sodium phosphate layer, packing each portion uniformly. On top of this prepared column place a pledget of fine glass wool, and pack lightly.

Column B—Pack a pledget of fine glass wool in the base of a second chromatographic tube of the size described under *Column A*. Mix intimately 3 g. of purified siliceous earth with 2.0 ml. of sulfamic acid solution (1 in 20), and transfer to the chromatographic tube in three portions, packing each portion uniformly. On top of this prepared column place a pledget of fine glass wool, and pack lightly.

Mount *Column A* directly over *Column B*.

Theophylline standard preparation—Transfer to a 100-ml. volumetric flask about 75 mg. of USP Theophylline Reference Standard, previously dried at 105° for 4 hours and accurately weighed, add 0.5 N sodium hydroxide to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with 0.5 N sodium hydroxide, and mix. Transfer 10.0 ml.

of this last solution to a third 100-ml. volumetric flask, dilute to volume with 0.5 *N* sodium hydroxide, and mix.

Ephedrine hydrochloride standard preparation—Transfer to a 100-ml. volumetric flask about 36 mg. of NF Ephedrine Hydrochloride Reference Standard, previously dried at 105° for 3 hours and accurately weighed, add 0.1 *N* hydrochloric acid to volume, and mix.

Phenobarbital standard preparation—Transfer to a 100-ml. volumetric flask about 120 mg. of USP Phenobarbital Reference Standard, previously dried at 105° for 2 hours and accurately weighed, add 0.5 *N* ammonium hydroxide to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with 0.5 *N* ammonium hydroxide, and mix. Transfer 10.0 ml. of this last solution to a third 100-ml. volumetric flask, dilute to volume with 0.5 *N* ammonium hydroxide, and mix.

Assay preparations—Add three 25-ml. portions of water-washed chloroform to *Column A*, allowing each portion to pass through both columns before adding the next portion. Discard the eluate from *Column B*, and separate the columns. Elute the theophylline and phenobarbital from *Column A* with 5 ml. of a 1 in 10 solution of glacial acetic acid in water-washed chloroform, followed by 150 ml. of a 1 in 100 solution of glacial acetic acid in water-washed chloroform, collecting the eluate in a 250-ml. beaker. Evaporate the eluate to about 25 ml., and then transfer to a 125-ml. separator containing 30 ml. of dilute sulfuric acid solution (1 in 5). Shake, allow the layers to separate, and transfer the chloroform layer to a second 125-ml. separator containing 30 ml. of dilute sulfuric acid solution (1 in 5). Shake, allow the layers to separate, and transfer the chloroform layer to a 250-ml. beaker. Repeat the extraction with four 25-ml. portions of chloroform. Retain the aqueous layers.

Evaporate the combined chloroform extracts to about 75 ml., transfer to a 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Evaporate a 20.0-ml. portion of this solution to dryness on a steam bath with the aid of a current of air. Dissolve the residue in 0.5 *N* ammonium hydroxide, quantitatively transfer to a 50-ml. volumetric flask, dilute to volume with 0.5 *N* ammonium hydroxide, and mix. Label this solution as the *Phenobarbital assay preparation*.

Transfer the aqueous layers to a 200-ml. volumetric flask, dilute to volume with 0.5 *N* sodium hydroxide, and mix. Transfer 3.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 0.5 *N* sodium hydroxide, and mix. Label this solution as the *Theophylline assay preparation*.

To *Column B* add 3 ml. of ammonium hydroxide, allow it to enter the column, and then add 100 ml. of water-washed chloroform, collecting the eluate in a 150-ml. beaker. Heat the eluate on a steam bath to expel the ammonia, then add 3 drops of hydrochloric acid, and continue the evaporation to about 10 ml. Evaporate the residual liquid to dryness with the aid of a current of air, without heating. Dissolve the residue in 0.1 *N* hydrochloric acid, and quantitatively transfer to a 25-ml. volumetric flask, filtering the solution through cotton previously washed with 0.1 *N* hydrochloric acid, into the flask. Dilute to volume with 0.1 *N* hydrochloric acid, and mix. Label this solution as the *Ephedrine hydrochloride assay preparation*.

Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, with a suitable spectrophotometer, at the maximum at about 275 mμ for the theophylline solutions, at about 257 mμ for the ephedrine hydrochloride solutions, and at about 240 mμ for the phenobarbital solutions, using a procedural blank prepared with the respective solvent employed for each solution in the reference cells. Record the absorbance of each *Standard preparation* as A_S and that of each *Assay preparation* as A_U.

Calculation for theophylline—Calculate the quantity, in mg., of $C_7H_8N_4O_2 . H_2O$ in the portion of Tablets taken by the formula $6.67C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Theophylline standard preparation*, calculated as the monohydrate.

Calculation for ephedrine hydrochloride—Calculate the quantity, in mg., of $C_{10}H_{15}NO . HCl$ in the portion of Tablets taken by the formula $0.025C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Ephedrine hydrochloride standard preparation*.

Calculation for phenobarbital—Calculate the quantity, in mg., of $C_{12}H_{12}N_2O_3$ in the portion of Tablets taken by the formula $0.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Phenobarbital standard preparation*.

Packaging and storage—Preserve Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets in tight containers.

Tablets available—Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets usually available contain the following amount of theophylline: 130 mg.; of ephedrine hydrochloride: 24 mg.; and of phenobarbital: 8 mg.

CATEGORY—Bronchodilator; sedative.

USUAL DOSE OF THEOPHYLLINE—**130** to **260 mg.** every 4 hours; OF EPHEDRINE HYDROCHLORIDE—**24** to **48 mg.** every 4 hours; OF PHENOBARBITAL—**8** to **16 mg.** every 4 hours.

Theophylline Tablets

Theophylline Tablets contain not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_7H_8N_4O_2 . H_2O$.

Identification—

A: Triturate a quantity of finely powdered Theophylline Tablets, equivalent to about 500 mg. of theophylline, with 10- and 5-ml. portions of solvent hexane, and discard the solvent hexane. Triturate the residue with two 10-ml. portions of a mixture of equal volumes of ammonia T.S. and water, and filter each time. Evaporate the combined filtrates to about 5 ml., neutralize if necessary with acetic acid, using litmus, then cool to about 15°, with stirring. Collect the precipitate on a filter, wash it well with cold water, and dry at 105° for 2 hours: the theophylline so obtained melts between 270° and 274°, page 814. Retain the remaining portion of the theophylline for use in *Identification tests B* and *C*.

B: To about 10 mg. of the theophylline obtained in *Identification test A*, contained in a porcelain dish, add 1 ml. of hydrochloric acid and 100 mg. of potassium chlorate, evaporate to dryness on a steam bath, and invert the dish over a vessel containing a few drops of ammonia T.S.: the residue acquires a purple color which is destroyed by solutions of alkalies.

C: Prepare a few ml. of a solution of theophylline from the theophylline obtained in *Identification test A*. Upon the addition of tannic acid T.S. to the solution a precipitate is produced which is soluble in an excess of the reagent.

Disintegration, page 878—The disintegration time limit for Theophylline Tablets is 30 minutes.

Weight variation, page 901—Theophylline Tablets meet the requirements of the weight variation test for tablets.

Assay—Place 20 Theophylline Tablets in a 200-ml. volumetric flask, add 50 ml. of water, and when the tablets have disintegrated add 50 ml. of ammonia T.S. Shake until no more dissolves, then add water to volume, mix well, and filter through a dry filter into a dry flask, rejecting the first 20 ml. of the filtrate. Transfer an accurately measured aliquot of the filtrate, equivalent to about 250 mg. of theophylline, to a 250-ml. conical flask, add 20.0 ml. of 0.1 *N* silver nitrate, and heat on a steam bath for 15 minutes. Filter through a filter crucible under reduced pressure, and wash the precipitate with three 10-ml. portions of water. Acidify the combined filtrate and washings with nitric acid, and add an excess of 3 ml. of the acid. Cool, add 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 19.82 mg. of $C_7H_8N_4O_2 . H_2O$.

Packaging and storage—Preserve Theophylline Tablets in well-closed containers.

Tablets available—Theophylline Tablets usually available contain the following amounts of theophylline: 100 and 200 mg.

CATEGORY—Smooth muscle relaxant; diuretic.

USUAL DOSE OF THEOPHYLLINE—**200 mg.** three or four times a day.

Theophylline Sodium Acetate

Theophylline Sodium Acetate is a hydrated mixture of $C_7H_7N_4NaO_2$ (sodium theophylline) and $C_2H_3NaO_2$ (sodium acetate) in approximately equimolecular proportions. It yields not less than 55.0 percent and not more than 65.0 percent of $C_7H_8N_4O_2$ (anhydrous theophylline).

Description—Theophylline Sodium Acetate occurs as a white, crystalline powder. It is odorless, and has a bitter, salty taste. It gradually absorbs carbon dioxide from the air with the liberation of free theophylline. Its solutions are alkaline to phenolphthalein T.S.

Solubility—Theophylline Sodium Acetate is soluble in water. It is insoluble in alcohol, in ether, and in chloroform.

Identification—

A: Dissolve about 1 g. of Theophylline Sodium Acetate in 20 ml. of warm water, and neutralize with diluted acetic acid: a white crystalline precipitate of theophylline is produced. Filter, wash the precipitate with small portions of cold water, and dry it at 105° for 1 hour: the theophylline so obtained melts between 270° and 274°, page 814. Retain the remaining residue for use in *Identification tests B* and *C*.

B: To about 10 mg. of the theophylline obtained in *Identification test A*, contained in a porcelain dish, add 1 ml. of hydrochloric acid and 100 mg. of potassium chlorate, evaporate to dryness on a steam bath, and invert the dish over a vessel containing a few drops of ammonia T.S.: the residue acquires a purple color which is destroyed by solutions of alkalies.

C: Prepare a few ml. of a solution of theophylline from the theophylline obtained in *Identification test A*. Upon the addition of tannic acid T.S. to the solution a precipitate is produced which is soluble in an excess of the reagent.

D: Suspend about 100 mg. of Theophylline Sodium Acetate in 2 ml. of 70 percent alcohol, add 5 drops of sulfuric acid, and boil gently: the mixture evolves the characteristic odor of ethyl acetate.

E: Ignite Theophylline Sodium Acetate: the residue colors a nonluminous flame intensely yellow and effervesces with acids.

Caffeine—Dissolve 500.0 mg. of Theophylline Sodium Acetate in 15 ml. of water in a small separator, add 10 ml. of sodium hydroxide T.S., and shake the mixture with 10.0 ml. of chloroform. Separate the chloroform layer, wash it with 2 ml. of water, evaporate the chloroform in a tared dish on a steam bath, and dry the residue at 80° for 1 hour: the residue weighs not more than 2.5 mg. (0.5 percent).

Assay—Place about 300 mg. of Theophylline Sodium Acetate, accurately weighed, in a 250-ml. conical flask, add 50 ml. of water and 8 ml. of ammonia T.S., and gently warm the mixture on a steam bath until complete solution is effected. Add 20.0 ml. of 0.1 *N* silver nitrate, mix, and continue to warm on the bath for 15 minutes. Filter through a filter crucible under reduced pressure while still warm, and wash the precipitate with three 10-ml. portions of water. Acidify the combined filtrate and washings with nitric acid, and add an excess of 3 ml. of the acid. Cool, add 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 18.02 mg. of $C_7H_8N_4O_2$.

Packaging and storage—Preserve Theophylline Sodium Acetate in tight containers.

CATEGORY—Smooth muscle relaxant.

USUAL DOSE RANGE—**200** to **300 mg.** three times a day.

Theophylline Sodium Acetate Tablets

Theophylline Sodium Acetate Tablets contain an amount of $C_7H_8N_4O_2$ (anhydrous theophylline) equivalent to not less than 53.0 percent and not more than 67.0 percent of the labeled amount of theophylline sodium acetate.

Identification—

A: Macerate a quantity of powdered Theophylline Sodium Acetate Tablets, equivalent to about 1 g. of theophylline, with 20 ml. of water and 1 ml. of ammonia T.S., and filter. Neutralize 15 ml. of the clear filtrate to litmus with diluted hydrochloric acid: a white precipitate of theophylline is formed. Retain the remaining 5 ml. of filtrate for use in *Identification test B*. Cool the precipitated mixture, collect the precipitate on a filter, wash it with small portions of cold water until free from chloride, and dry at 105° for 1 hour: the theophylline so obtained melts between 270° and 274°, page 814. Retain the remaining portion of the theophylline for *Identification tests C* and *D*.

B: To the filtrate retained in *Identification test A* add 3 ml. of alcohol and 0.5 ml. of sulfuric acid, and boil gently: the odor of ethyl acetate is evolved.

C: To about 10 mg. of the theophylline obtained in *Identification test A*, contained in a porcelain dish, add 1 ml. of hydrochloric acid and 100 mg. of potassium chlorate, evaporate to dryness on a steam bath, and invert the dish over a vessel containing a few drops of ammonia T.S.: the residue acquires a purple color which is destroyed by solutions of alkalies.

D: Prepare a few ml. of a solution of theophylline from the theophylline obtained in *Identification test A*. Upon the addition of tannic acid T.S. to the solution a precipitate is produced which is soluble in an excess of the reagent.

Disintegration, page 878—The disintegration time limit for Theophylline Sodium Acetate Tablets is 30 minutes.

Weight variation, page 901—Theophylline Sodium Acetate Tablets meet the requirements of the weight variation test for tablets.

Assay—Place 20 Theophylline Sodium Acetate Tablets in a 200-ml. volumetric flask, add 50 ml. of water and 10 ml. of ammonia T.S., and allow to stand with frequent shaking for 30 minutes or until no more dissolves. Dilute to volume with water, mix well, and filter. Transfer an accurately measured aliquot of the filtrate, equivalent to about 350 mg. of theophylline sodium acetate, to a 250-ml. conical flask, and add 8 ml. of ammonia T.S. and 20.0 ml. of 0.1 *N* silver nitrate. Heat on a steam bath for 15 minutes, then filter through a filter crucible under reduced pressure, and wash the precipitate with three 10-ml. portions of water. Acidify the combined filtrate and washings with nitric acid, and add an excess of 3 ml. of the acid. Cool, add 2 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 18.02 mg. of $C_7H_8N_4O_2$.

Packaging and storage—Preserve Theophylline Sodium Acetate Tablets in tight containers.

Tablets available—Theophylline Sodium Acetate Tablets usually available contain the following amounts of theophylline sodium acetate: 100 and 200 mg.

Category and Dose—See Theophylline Sodium Acetate.

Theophylline Sodium Glycinate*

Theophylline Sodium Glycinate is an equilibrium mixture containing $C_7H_7N_4NaO_2$ (sodium theophylline) and $C_2H_5NO_2$ (aminoacetic acid) in approximately equimolecular proportions buffered with an additional mole of aminoacetic acid. Dried at 105° for 4 hours, it contains not less than 49.0 percent and not more than 52.0 percent of $C_7H_8N_4O_2 . H_2O$ (theophylline).

Description—Theophylline Sodium Glycinate occurs as a white, crystalline powder. It has a slight ammoniacal odor, and a bitter taste.

Solubility—Theophylline Sodium Glycinate is freely soluble in water. It is very slightly soluble in alcohol and practically insoluble in chloroform.

Identification—

A: Dissolve about 1 g. of Theophylline Sodium Glycinate in 20 ml. of warm water, and neutralize the solution with acetic acid: a white crystalline precipitate of theophylline is formed. Filter, wash the precipitate with small portions of cold water, and dry it at 105° for 1 hour: the theophylline so obtained melts between 270° and 274°, page 814. Retain the remaining portion of the theophylline for *Identification tests B* and *C*.

B: To about 10 mg. of the theophylline obtained in *Identification test A*, contained in a porcelain dish, add 1 ml. of hydrochloric acid and 100 mg. of potassium chlorate, evaporate to dryness on a steam bath, and invert the dish over a vessel containing a few drops of ammonia T.S.: the residue acquires a purple color which is destroyed by solutions of alkalies.

C: Prepare a few ml. of a solution of theophylline from the theophylline obtained in *Identification test A*. Upon the addition of tannic acid T.S. to the solution a precipitate is produced which is soluble in an excess of the reagent.

D: Ignite Theophylline Sodium Glycinate: the residue colors a nonluminous flame intensely yellow and effervesces with acids.

pH, page 824—The pH of a saturated solution of Theophylline Sodium Glycinate is between 8.5 and 9.5.

Loss on drying, page 814—Dry Theophylline Sodium Glycinate at 105° for 4 hours: it loses not more than 2 percent of its weight.

Assay—Weigh accurately about 1 g. of Theophylline Sodium Glycinate, previously dried at 105° for 4 hours, and transfer it to a 500-ml. conical flask. Add 100 ml. of water and 16 ml. of ammonia T.S., and warm on a steam bath until all of the Theophylline Sodium Glycinate is in solution. Then add 50.0 ml. of 0.1 *N* silver nitrate, mix well, and continue to warm on a steam bath for 15 minutes. While the solution is still warm, filter off the precipitate, and wash the precipitate and filter with four 20-ml. portions of warm water, adding the washings to the filtrate. Acidify the combined washings and filtrate with nitric acid, and add an excess of 7 ml. of the acid. Cool, add 4 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 19.82 mg. of $C_7H_8N_4O_2 . H_2O$.

Packaging and storage—Preserve Theophylline Sodium Glycinate in tight containers.

Category—Smooth muscle relaxant.

Usual dose—**300 mg.** every 4 to 6 hours.

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* Patented. See notice, page ii.

Theophylline Sodium Glycinate Tablets

Theophylline Sodium Glycinate Tablets contain an amount of $C_7H_8N_4O_2 . H_2O$ (theophylline) equivalent to not less than 47.0 percent and not more than 54.0 percent of the labeled amount of theophylline sodium glycinate.

Identification—Triturate a quantity of finely powdered Theophylline Sodium Glycinate Tablets, equivalent to about 500 mg. of theophylline, with 10- and 15-ml. portions of solvent hexane and discard the solvent hexane. Triturate the residue with two 10-ml. portions of a mixture of equal volumes of ammonia T.S. and water, and filter each time. Evaporate the combined filtrates to about 5 ml., neutralize if necessary with acetic acid, using litmus, then cool to about 15°, with stirring. Collect the precipitate on a filter, wash it well with cold water, and dry at 105° for 1 hour: the theophylline so obtained melts between 270° and 274°, page 814. Retain the remaining portion of the theophylline for *Identification tests B* and *C*.

B: To about 10 mg. of the theophylline obtained in *Identification test A*, contained in a porcelain dish, add 1 ml. of hydrochloric acid and 100 mg. of potassium chlorate, evaporate to dryness on a steam bath, and invert the dish over a vessel containing a few drops of ammonia T.S.: the residue acquires a purple color which is destroyed by solutions of alkalies.

C: Prepare a few ml. of a solution of theophylline from the theophylline obtained in *Identification test A*. Upon the addition of tannic acid T.S. to the solution a precipitate is produced which is soluble in an excess of the reagent.

Disintegration, page 878—The disintegration time limit for Theophylline Sodium Glycinate Tablets is 30 minutes.

Weight variation, page 901—Theophylline Sodium Glycinate Tablets meet the requirements of the weight variation test for tablets.

Assay—Place 20 Theophylline Sodium Glycinate Tablets in a 200-ml. volumetric flask, add 50 ml. of water, and proceed as directed in the *Assay* under *Theophylline Tablets*, page 697, beginning with "... and when the tablets have disintegrated add 50 ml. of ammonia T.S. ..." Each ml. of 0.1 *N* silver nitrate is equivalent to 19.82 mg. of $C_7H_8N_4O_2 . H_2O$.

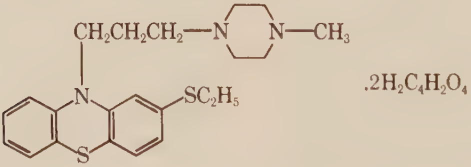
Packaging and storage—Preserve Theophylline Sodium Glycinate Tablets in well-closed containers.

Tablets available—Theophylline Sodium Glycinate Tablets usually available contain the following amounts of theophylline sodium glycinate: 150, 300, and 330 mg.

CATEGORY and DOSE—See Theophylline Sodium Glycinate.

Thiamylal, Sodium, for Injection, page 661

Thiethylperazine Maleate*



2-(Ethylthio)-10-[3-(4-methyl-1-piperazinyl)propyl]phenothiazine Maleate (1:2)

$C_{22}H_{29}N_3S_2 . 2C_4H_4O_4$ Mol. wt. 631.77

Thiethylperazine Maleate contains not less than 98.0 percent and not more than 101.5 percent of $C_{22}H_{29}N_3S_2 . 2C_4H_4O_4$, calculated on the dried basis.

Description—Thiethylperazine Maleate occurs as a slightly yellowish, voluminous powder having a bitter taste. It is odorless or has not more than a slight odor. It melts at about 183° with decomposition.

Solubility—Thiethylperazine Maleate is very slightly soluble in water. It is slightly soluble in methanol, and is practically insoluble in chloroform.

Identification—

A: To 2 ml. of Thiethylperazine Maleate solution (1 in 5000) add 2 ml. of nitric acid: a blue color is produced, which disappears and then turns to red-violet.

B: Suspend about 200 mg. of Thiethylperazine Maleate in 5 ml. of water, and add 2 ml. of stronger ammonia water. Extract the mixture with three 10-ml. portions of chloroform, discarding the extracts. Acidify the aqueous layer with about 10 ml. of diluted sulfuric acid, and allow the solution to cool to room temperature. Add 50 ml. of ether, mix vigorously, and discard the aqueous layer. Filter the ether layer through anhydrous sodium sulfate, previously moistened with ether, and evaporate the filtrate to dryness on a steam bath: the residue of maleic acid so obtained melts between 131° and 138°, page 814.

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* Patented. See notice, page ii.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Thiethylperazine Maleate, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Thiethylperazine Maleate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Thiethylperazine Maleate in water exhibits maxima and minima at the same wavelengths as that of NF Thiethylperazine Maleate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 263 mμ, do not differ by more than 3 percent.

pH, page 824—Dissolve 100 mg. of Thiethylperazine Maleate in 100 ml. of water, warming if necessary to effect solution. The pH of this solution is between 2.8 and 3.8.

Loss on drying, page 814—Dry Thiethylperazine Maleate at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Thiethylperazine Maleate yields not more than 0.1 percent of residue on ignition.

Selenium—A *Test preparation* prepared with 100 mg. of Thiethylperazine Maleate and 100 mg. of magnesium oxide meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Assay—Transfer about 250 mg. of Thiethylperazine Maleate, accurately weighed, to a suitable titration vessel, add 30 ml. of glacial acetic acid, and warm on a steam bath to effect solution. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank titration, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 31.59 mg. of $C_{22}H_{29}N_3S_2 \cdot 2C_4H_4O_4$.

Packaging and storage—Preserve Thiethylperazine Maleate in tight, light-resistant containers.

CATEGORY—Antiemetic.

USUAL DOSE RANGE—Oral and intramuscular, **10** to **30 mg.** daily.

Thiethylperazine Maleate Tablets

Thiethylperazine Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{29}N_3S_2 \cdot 2C_4H_4O_4$.

Identification—Digest a quantity of powdered Thiethylperazine Maleate Tablets, equivalent to about 10 mg. of thiethylperazine maleate, with 50 ml. of water, and filter: the solution so obtained responds to *Identification test A* under *Thiethylperazine Maleate,* page 700.

Disintegration, page 878—The disintegration time limit for Thiethylperazine Maleate Tablets is 20 minutes.

Content uniformity, *Method I,* page 799—Thiethylperazine Maleate Tablets meet the requirements of the content uniformity test for tablets.

Assay—[NOTE: Conduct this Assay with a minimum exposure to light.]

Ammoniacal chloroform—Shake 300 ml. of chloroform with 12 ml. of stronger ammonia water in a separator, slowly filter the lower layer through a glass wool filter layered over with anhydrous sodium sulfate and discard the aqueous layer. Use the filtrate as directed under *Assay preparation.*

Standard preparation—Transfer about 20 mg. of NF Thiethylperazine Maleate Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add *Ammoniacal chloroform* to volume, and mix. Transfer 5.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with *Ammoniacal chloroform,* and mix.

Assay preparation—Weigh and finely powder not less than 20 Thiethylperazine Maleate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 8 mg. of thiethylperazine maleate, to a 250-ml. glass-stoppered flask, add 150 ml. of dilute sulfuric acid (1 in 350), and shake for 15 minutes. Filter the mixture through a pledget of glass wool into a 200-ml. volumetric flask, wash the original flask and filter with sufficient dilute sulfuric acid (1 in 350) to bring to volume, and mix. Transfer 25.0 ml. of the solution to a 125-ml. separator, extract with 25 ml. of solvent hexane, and transfer the aqueous phase to a second 125-ml. separator. Extract the solvent hexane phase with two 5-ml. portions of dilute sulfuric acid (1 in 350), collecting the acid extracts in the second 125-ml. separator containing the original aqueous phase. Discard the solvent hexane phase. To the combined aqueous acid solution add 2 ml. of ammonia T.S., and extract with two 40-ml. portions, followed by one 15-ml. portion of chloroform, filtering the extracts through glass wool layered over with a small amount of anhydrous sodium sulfate into a 100-ml. volumetric flask. Wash the filter with sufficient *Ammoniacal chloroform* to bring to volume, and mix.

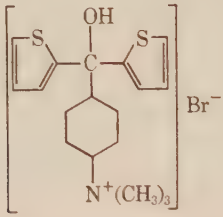
Procedure—Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 267 mμ, with a suitable spectrophotometer, using *Ammoniacal chloroform* as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{22}H_{29}N_3S_2 . 2C_4H_4O_4$ in the portion of Tablets taken by the formula $0.8C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Thiethylperazine Maleate Tablets in tight, light-resistant containers.

Tablets available—Thiethylperazine Maleate Tablets usually available contain the following amount of thiethylperazine maleate: 10 mg.

CATEGORY and DOSE—See Thiethylperazine Maleate.

Thihexinol Methylbromide*



[4-(Hydroxydi-2-thienylmethyl)cyclohexyl]trimethylammonium Bromide

$C_{18}H_{26}BrNOS_2$ Mol. wt. 416.45

Thihexinol Methylbromide, dried at 105° for 3 hours, contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{26}BrNOS_2$.

Description—Thihexinol Methylbromide occurs as a white to creamy white, crystalline powder. It melts at about 235° with decomposition.

Solubility—Thihexinol Methylbromide is sparingly soluble in water and in chloroform. It is soluble in alcohol and is very slightly soluble in acetone and in ether.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Thihexinol Methylbromide, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Thihexinol Methylbromide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 25,000 solution of Thihexinol Methylbromide in methanol exhibits maxima and minima at the same wavelengths as that of NF Thihexinol Methylbromide Reference Standard, similarly measured, and the respective absorptivities, at the point of maximum absorbance occurring at about 234 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Thihexinol Methylbromide at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Thihexinol Methylbromide yields not more than 0.15 percent of residue on ignition.

Selenium—A *Test Preparation* of 200 mg. of Thihexinol Methylbromide meets the requirement of the *Selenium Limit Test*, page 865 (30 parts per million).

Assay—Dissolve about 800 mg. of Thihexinol Methylbromide, previously dried at 105° for 3 hours and accurately weighed, in a mixture of 50 ml. of glacial acetic acid, 10 ml. of mercuric acetate T.S., and 10 ml. of acetic anhydride, warming slightly if necessary to effect solution. Add 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 41.65 mg. of $C_{18}H_{26}BrNOS_2$.

Packaging and storage—Preserve Thihexinol Methylbromide in tight, light-resistant containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**15 mg.** four times a day.

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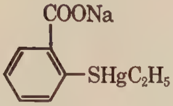
* Patented. See notice, page ii.

Thimerosal



Sodium [(*o*-Carboxyphenyl)thio]ethylmercury

$C_9H_9HgNaO_2S$ Mol. wt. 404.81

Thimerosal, dried to constant weight in vacuum over phosphorus pentoxide, contains not less than 97.0 percent and not more than 101.0 percent of $C_9H_9HgNaO_2S$.

Description—Thimerosal occurs as a light cream-colored, crystalline powder. It has a slight characteristic odor. It is affected by light. The pH of a 1 in 100 solution is about 6.7.

Solubility—Thimerosal is freely soluble in water and soluble in alcohol. It is almost insoluble in ether and in benzene.

Identification—

A: To a solution of Thimerosal (1 in 20) add a slight excess of diluted sulfuric acid: a white precipitate is formed.

B: To a solution of Thimerosal (1 in 100) add a few drops of silver nitrate T.S.: a white precipitate is formed.

C: To a solution of Thimerosal (1 in 100) add a few drops of lead acetate T.S.: a white precipitate is formed.

D: To a solution of Thimerosal (1 in 100) add cupric sulfate T.S.: a green precipitate is formed.

Loss on drying, page 814—Dry Thimerosal to constant weight in vacuum over phosphorus pentoxide: it loses not more than 0.5 percent of its weight.

Ether-soluble substances—Shake 500 mg. of Thimerosal, accurately weighed, with 20 ml. of absolute ether for 10 minutes. Filter, evaporate the ether in a tared container, dry the residue in vacuum over phosphorus pentoxide, and weigh. The weight of the residue does not exceed 4 mg. (0.8 percent).

Mercury ions—To a solution of Thimerosal (1 in 100) add an equal volume of ammonium sulfide T.S.: a white precipitate is formed, but no blackening occurs after standing 48 hours in the dark.

Readily carbonizable substances, page 856—Dissolve about 200 mg. of Thimerosal in 5 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid J.

Assay—

Standard preparation—Transfer about 100 mg. of NF Thimerosal Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add 25 ml. of water, and mix thoroughly to dissolve. Dilute to volume with water, and mix.

Assay preparation—Transfer about 100 mg. of Thimerosal, accurately weighed, to a 100-ml. volumetric flask, add 25 ml. of water, and mix thoroughly to dissolve. Dilute to volume with water, and mix.

Procedure—Concomitantly determine the absorbances of the solutions at the mercury reflectance line of 2536.5 Å, with a suitable atomic absorption spectrophotometer (see page 866) equipped with a mercury hollow cathode lamp and an air-acetylene flame, using water as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_9H_9HgNaO_2S$ in the Thimerosal taken by the formula $100C \times (A_U/A_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation.*

Packaging and storage—Preserve Thimerosal in tight, light-resistant containers.

CATEGORY—Local anti-infective.

APPLICATION—Topically as a 0.1 percent solution or tincture.

Thimerosal Aerosol

Thimerosal Aerosol is an alcoholic solution of thimerosal mixed with suitable propellants in a pressurized container. It contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of $C_9H_9HgNaO_2S$. The preparation may be colored with one or more color additives, certified by the federal Food and Drug Administration for use in drugs.

Monoethanolamine	292 mcg.
Edetic Acid	21.1 mcg.
Purified Water	6.1 ml.
Thimerosal	1.0 g.
Acetone	100 ml.
Alcohol, a sufficient quantity,	
To make	1000 ml.

Caution: Manufacture and store Thimerosal Aerosol in glass or suitably resistant metal containers.

To 433 ml. of alcohol add the monoethanolamine and edetic acid. Dissolve the thimerosal in 6.1 ml. of purified water, and add to the alcohol mixture. Add the acetone and a sufficient quantity of alcohol to make 1000 ml. Mix thoroughly and filter. Add sufficient propellant during filling.

Identification—

A: To about 10 ml. of a sample of solution sprayed into a suitable container from Thimerosal Aerosol, add 10 ml. of water, and heat on a steam bath until the odor of alcohol is no longer noticeable. Cool, and pass hydrogen sulfide through the solution: no black discoloration or black precipitate is formed.

B: To 15 ml. of a sample of solution sprayed into a suitable container from Thimerosal Aerosol, add 15 ml. of water, heat on a steam bath until the odor of alcohol is no longer noticeable, and add 2 drops of bromine. Mix with 1.5 ml. of dilute hydrochloric acid, filter, evaporate the excess bromine with a stream of air, and pass hydrogen sulfide through the filtrate: a black precipitate is formed.

Other requirements—Thimerosal Aerosol meets the requirements for *Leak Testing* and *Pressure Testing* under *Aerosols,* page 770.

Assay—

Standard preparations—Transfer about 47 mg., 59 mg., and 72 mg. of NF Thimerosal Reference Standard, accurately weighed, to separate 50-ml. volumetric flasks. Add 31.1 mg. of monoethanolamine and 35.0 ml. of alcohol to each flask, dilute each to volume with water, and mix to dissolve.

Assay preparation—Weigh accurately a filled Thimerosal Aerosol container, and record the weight. Place the container in a dry ice-alcohol bath, and cool for 60 minutes. Remove the container from the bath, and carefully remove the spray cap with wire cutters, taking precautions to save all pieces of the spray head and cap. With the aid of three 5-ml. portions of water, transfer the contents of the container to a beaker previously chilled in the bath. Dry the rinsed empty container and all of its parts in an oven at 105° for 2 hours, cool, and weigh. Calculate the weight of the container contents. Add a few boiling chips to the beaker, and carefully stir to help evaporate the propellant. After the bulk of the propellant has evaporated, place the beaker on a steam bath, evaporate the alcohol and acetone, and cool. Quantitatively transfer the residual liquid with the aid of 35.0 ml. of alcohol to a 50-ml. volumetric flask, dilute to volume with water, and mix.

Procedure—Concomitantly determine the absorbances of the solutions at the mercury reflectance line of 2536.5 Å, with a suitable atomic absorption spectrophotometer (see page 866) equipped with a mercury hollow cathode lamp and an air-acetylene flame, using water as the blank. Plot the absorbances of the *Standard preparations* vs. concentration of thimerosal, in mg. per ml., and from the curve so obtained determine the concentration, C, of the *Assay preparation*. Calculate the quantity, in mg., of $C_9H_9HgNaO_2S$ in the Aerosol by the formula $50C$.

Alcohol content—Open a Thimerosal Aerosol container and remove the propellant as directed for *Assay preparation* in the *Assay,* continuing until the bulk of the propellant has evaporated. Determine the alcohol content of the sample thus prepared by the gas-liquid chromatographic procedure, page 772, using methyl ethyl ketone as the internal standard. Thimerosal Aerosol contains from 18.7 to 25.3 percent (w/w) of C_2H_5OH.

Packaging and storage—Preserve Thimerosal Aerosol in tight, light-resistant pressurized containers, and avoid exposure to excessive heat.

CATEGORY and APPLICATION—See Thimerosal.

Thimerosal Solution

Thimerosal Solution contains, in each 100 ml., not less than 95 mg. and not more than 105 mg. of $C_9H_9HgNaO_2S$. The preparation may be colored with one or more color additives, certified by the federal Food and Drug Administration for use in drugs.

Thimerosal	1 g.
Ethylenediamine	200 mg.
Monoethanolamine	1 g.
Sodium Chloride	8 g.
Sodium Borate	1.4 g.
Purified Water, a sufficient quantity,	
To make	1000 ml.

Caution: Manufacture and store Thimerosal Solution in glass or suitably resistant metal containers.

To 250 ml. of purified water add the ethylenediamine and the monoethanolamine. Dissolve the sodium chloride, sodium borate, and thimerosal in this solution, and add sufficient purified water to make 1000 ml. Mix thoroughly and filter.

Description—Thimerosal Solution is a clear liquid having a slight characteristic odor. It is affected by light.

Identification—

A: Pass hydrogen sulfide through 50 ml. of Thimerosal Solution: no black discoloration or black precipitate is formed.

B: To 50 ml. of Thimerosal Solution add 3 or 4 drops of bromine, mix well, and warm on a steam bath to expel the excess bromine. Add 5 ml. of diluted hydrochloric acid, filter, and pass hydrogen sulfide through the filtrate: a black precipitate is formed.

C: To 1 ml. of Thimerosal Solution add 9 ml. of water, mix, and add 1 ml. of cupric sulfate T.S.: a green color immediately develops followed by the gradual precipitation of flocculent, greenish brown particles.

Specific gravity, page 866—The specific gravity of Thimerosal Solution is not less than 1.004 and not more than 1.010.

pH, page 824—The pH of Thimerosal Solution is between 9.8 and 10.3.

Assay—

Standard preparation—To each of two 100-ml. volumetric flasks add 28 mg. of ethylenediamine, 100 mg. of monoethanolamine, and 25 ml. of water, and mix to dissolve. Add to each flask 800 mg. of sodium chloride and 140 mg. of sodium borate, and mix. To one of the flasks add 95 mg. of NF Thimerosal Reference Standard. Dilute each flask to volume with water, and mix to dissolve.

Assay preparation—Use Thimerosal Solution undiluted.

Procedure—Concomitantly determine the absorbances of the solutions at the mercury reflectance line of 2536.5 Å, with a suitable atomic absorption spectrophotometer (see page 866) equipped with a mercury hollow cathode lamp and an air-acetylene flame, using water as the blank. Plot the absorbances of the *Standard preparation* vs. concentration of thimerosal, in mg. per ml., and from the curve so obtained determine the concentration, *C*, of $C_9H_9HgNaO_2S$ in the *Assay preparation*, in mg. per ml.

Packaging and storage—Preserve Thimerosal Solution in tight, light-resistant containers, and avoid exposure to excessive heat.

CATEGORY and APPLICATION—See Thimerosal.

Thimerosal Tincture

Thimerosal Tincture contains, in each 100 ml., not less than 95 mg. and not more than 105 mg. of $C_9H_9HgNaO_2S$. The preparation may be colored with one or more color additives, certified by the federal Food and Drug Administration for use in drugs.

Thimerosal	1 g.
Alcohol	525 ml.
Acetone	100 ml.
Ethylenediamine	200 mg.
Monoethanolamine	1 g.
Purified Water, a sufficient quantity,	
To make	1000 ml.

Caution: Manufacture and store Thimerosal Tincture in glass or suitably resistant metal containers.

To 250 ml. of purified water add the ethylenediamine and the monoethanolamine, and dissolve the thimerosal in this mixture. Add the alcohol, acetone, and sufficient purified water to make 1000 ml. Mix thoroughly and filter.

Description—Thimerosal Tincture is a transparent, mobile liquid with the characteristic odor of alcohol and acetone. It is affected by light.

Identification—

A: Heat 25 ml. of Thimerosal Tincture on a steam bath until the odor of alcohol and acetone is no longer noticeable. Cool, and pass hydrogen sulfide through the solution: no black discoloration or black precipitate is formed.

B: Evaporate 50 ml. of Thimerosal Tincture on a steam bath to a volume of approximately 20 ml., cool, and add 3 or 4 drops of bromine. Add 5 ml. of diluted hydrochloric acid, filter, and pass hydrogen sulfide through the filtrate: a black precipitate is formed.

Specific gravity, page 866—The specific gravity of Thimerosal Tincture is not less than 0.905 and not more than 0.915.

Assay—

Standard preparation—To each of two 100-ml. volumetric flasks add 28 mg. of ethylenediamine, 100 mg. of monoethanolamine, 25 ml. of water, 52.2 ml. of alcohol, and 10.0 ml. of acetone. Add to each flask the proper amount of any other constituents which would be present in the product being tested, and mix to dissolve. To one of the flasks add 95.0 mg. of NF Thimerosal Reference Standard, and to the other add 105.0 mg. of the Reference Standard. Dilute to volume with water, and mix to dissolve.

Assay preparation—Use Thimerosal Tincture undiluted.

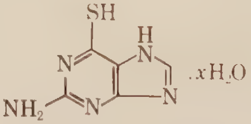
Procedure—Transfer 25.0 ml. of the *Assay preparation* and of each of the *Standard preparations* to separate 50-ml. beakers, and heat on a steam bath until the alcohol and acetone have completely evaporated. Transfer each solution to a separate 25-ml. volumetric flask, dilute to volume with water, and mix. Concomitantly determine the absorbance of each solution at the mercury reflectance line of 2536.5 Å, with a suitable atomic absorption spectrophotometer (see page 866) equipped with a mercury hollow cathode lamp and an air-acetylene flame, using water as the blank. Plot the absorbances of the *Standard preparations* vs. concentration of thimerosal, in mg. per ml., and from the curve so obtained determine the concentration, *C*, of $C_9H_9HgNaO_2S$ in the *Assay preparation*, in mg. per ml.

Alcohol content—Determine the alcohol content by the gas-liquid chromatographic procedure, page 772, using methyl ethyl ketone as the internal standard. Thimerosal Tincture contains from 47 to 53 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Thimerosal Tincture in tight, light-resistant containers, and avoid exposure to excessive heat.

Category and Application—See Thimerosal.

Thioguanine*



2-Aminopurine-6-thiol

$C_5H_5N_5S . xH_2O$ Mol. wt. (anhydrous) 167.20

Thioguanine is anhydrous or contains one-half molecule of water of hydration. After drying at 105° in vacuum for 5 hours, it contains not less than 97.0 percent and not more than 100.5 percent of $C_5H_5N_5S$.

Description—Thioguanine occurs as a pale yellow, crystalline powder. It is odorless or is practically odorless.

Solubility—Thioguanine is insoluble in water, in alcohol, and in chloroform. It is freely soluble in dilute solutions of alkali hydroxides.

Identification—Mix about 10 mg. of Thioguanine with an equal amount of sodium formate in a small test tube, and gradually heat until the mixture is melted. Cover the mouth of the tube with a piece of filter paper moistened with lead acetate T.S., and heat carefully: a gray or black stain is formed on the paper.

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* Patented. See notice, page ii.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Thioguanine, previously dried in vacuum at 105° for 5 hours, exhibits maxima only at the same wavelengths as that of NF Thioguanine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Thioguanine, prepared as directed in the *Assay,* exhibits maxima and minima at the same wavelengths as that of NF Thioguanine Reference Standard, similarly measured.

Loss on drying, page 814—Dry Thioguanine in vacuum at 105° for 5 hours: it loses not more than 6 percent of its weight.

Nitrogen—Determine the nitrogen content of Thioguanine as directed under *Nitrogen Determination, Method II,* page 821, using about 100 mg., accurately weighed. Each ml. of 0.1 *N* sulfuric acid is equivalent to 1.401 mg. of nitrogen. The amount of nitrogen found, calculated on the dried basis, is not less than 40.6 percent and not more than 43.1 percent.

Phosphorus-containing substances—

Ammonium molybdate solution—Dissolve 8.3 g. of ammonium molybdate in 40 ml. of water, add 33 ml. of 10 *N* sulfuric acid, dilute to 100.0 ml. with water, and mix. This solution is stable for approximately two weeks.

Procedure—Transfer 50.0 mg. of Thioguanine, accurately weighed, to a large test tube, add 1 ml. of 10 *N* sulfuric acid, and heat in a boiling water bath for 5 minutes. Cautiously add nitric acid, dropwise, continue heating until the mixture becomes colorless, and then heat for 1 minute longer. Cool, dilute to about 10 ml. with water, and quantitatively transfer the solution to a 25-ml. volumetric flask with the aid of a few ml. of water. To the flask add 0.75 ml. of *Ammonium molybdate solution* and 1.0 ml. of aminonaphtholsulfonic acid T.S., dilute to volume with water, and mix. Determine the absorbance of this solution in a 1-cm. cell, with a suitable spectrophotometer at about 620 mμ, using a reagent blank to set the instrument: the absorbance is not greater than that produced by 1.5 ml. of a solution of monobasic potassium phosphate prepared in water to contain 10 mcg. of phosphate (PO_4) in each ml., similarly measured (0.03 percent).

Selenium—A *Test Preparation* prepared with 200 mg. of Thioguanine meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Free sulfur—Dissolve 50 mg. of Thioguanine in 5 ml. of sodium hydroxide T.S.: the solution is clear.

Assay—Transfer about 100 mg. of Thioguanine, previously dried at 105° in vacuum for 5 hours and accurately weighed, to a 100-ml. volumetric flask, dissolve in a mixture of 15 ml. of water and 1.5 ml. of sodium hydroxide T.S., dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Finally, transfer 5.0 ml. of the last solution to a third 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Thioguanine Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells at the maximum at about 348 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_5H_5N_5S$ in the Thioguanine taken by the formula $20C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Thioguanine in tight containers.

Labeling—Label Thioguanine to indicate its state of hydration.

CATEGORY—Antineoplastic.

USUAL DOSE—Initial, **2 mg. per kg.** of body weight per day. Maintenance, to be determined according to the needs of the patient.

Thioguanine Tablets

Thioguanine Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_5H_5N_5S$.

Identification—A portion of finely powdered Thioguanine Tablets, equivalent to about 5 mg. of thioguanine, responds to the *Identification test* under *Thioguanine,* page 706.

Disintegration, page 878—The disintegration time limit for Thioguanine Tablets is 15 minutes.

Content uniformity, *Method I,* page 799—Thioguanine Tablets meet the requirements of the content uniformity test for tablets.

Assay—

Standard preparations—Prepare by quantitative and stepwise dilution a solution in 0.1 *N* sodium hydroxide of NF Thioguanine Reference Standard, accurately weighed, containing approximately 80 mcg. per ml. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 1 *N* hydrochloric acid, mix, and label as *Acidic standard preparation*. Transfer another 5.0-ml. portion of the solution to a second 100-ml. volumetric flask, add 10.0 ml. of sodium hydroxide T.S., dilute to volume with water, mix, and label as *Basic standard preparation*.

Assay preparations—Weigh and finely powder not less than 20 Thioguanine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg. of thioguanine, to a 500-ml. volumetric flask, add 50 ml. of sodium hydroxide T.S., and allow to stand for 10 minutes with frequent swirling. Dilute to volume with water, mix, and filter a portion of the solution through a pledget of glass wool. Transfer 5.0 ml. of the filtrate to a 100-ml. volumetric flask, dilute to volume with 1 *N* hydrochloric acid, mix, and label as *Acidic assay preparation*. Transfer another 5.0-ml. portion of the filtrate to a second 100-ml. volumetric flask, add 10.0 ml. of sodium hydroxide T.S., dilute to volume with water, mix, and label as *Basic assay preparation*.

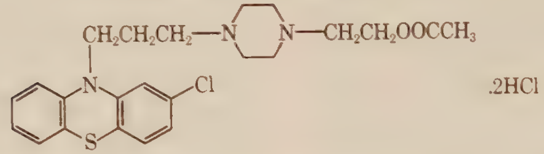
Procedure—Concomitantly determine the absorbance of the acidic *Assay preparation* and the acidic *Standard preparation* at the point of maximum absorbance at about 348 mμ, in 1-cm. cells, with a suitable spectrophotometer, using the basic *Assay preparation* and the basic *Standard preparation* respectively as the blank solutions. Calculate the quantity, in mg., of $C_5H_5N_5S$ in the portion of Tablets taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and A_U and A_S are the absorbances of the acidic *Assay preparation* and the acidic *Standard preparation*, respectively.

Packaging and storage—Preserve Thioguanine Tablets in tight containers.

Tablets available—Thioguanine Tablets usually available contain the following amount of thioguanine: 40 mg.

CATEGORY and DOSE—See Thioguanine.

Thiopropazate Hydrochloride*



4-[3-(2-Chlorophenothiazin-10-yl)propyl]-1-piperazineethanol Acetate Dihydrochloride

$C_{23}H_{28}ClN_3O_2S.2HCl$ Mol. wt. 518.94

Thiopropazate Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent of $C_{23}H_{28}ClN_3O_2S.2HCl$, calculated on the anhydrous basis.

Description—Thiopropazate Hydrochloride occurs as a white, odorless, crystalline powder. It is stable in air.

Solubility—Thiopropazate Hydrochloride is freely soluble in water. It is soluble in alcohol, very slightly soluble in acetone, and insoluble in ether.

Melting range, page 814—Thiopropazate Hydrochloride melts between 226° and 232°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Thiopropazate Hydrochloride, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Thiopropazate Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Thiopropazate Hydrochloride in methanol exhibits maxima and minima at the same wavelengths as that of NF Thiopropazate Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the anhydrous basis, at the point of maximum absorbance, occurring at about 255 mμ, do not differ by more than 3 percent.

Water, page 900—Determine the water content of Thiopropazate Hydrochloride by the titrimetric method: not more than 1.5 percent is found.

Residue on ignition, page 858—Thiopropazate Hydrochloride yields not more than 0.3 percent of residue on ignition.

Assay—Dissolve about 300 mg. of Thiopropazate Hydrochloride, accurately weighed, in 75 ml. of glacial acetic acid. Add 10 ml. of mercuric acetate T.S., and titrate 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 25.95 mg. of $C_{23}H_{28}ClN_3O_2S.2HCl$.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Thiopropazate Hydrochloride in well-closed containers protected from light.

CATEGORY—Tranquilizer (major).

USUAL DOSE—**10 mg.** three times a day, adjusted upward or downward in daily increments of 10 mg., at intervals of 3 or 4 days, according to response.

USUAL DOSE RANGE—**5** to **10 mg.**

Thiopropazate Hydrochloride Tablets

Thiopropazate Hydrochloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{23}H_{28}ClN_3O_2S.2HCl$.

Identification—Transfer a portion of finely powdered Thiopropazate Hydrochloride Tablets, equivalent to about 100 mg. of thiopropazate hydrochloride, to a 50-ml. glass-stoppered cylinder, and add 50 ml. of ether which has been saturated with ammonia. Mix, allow to stand for 30 minutes with occasional shaking, and wash the ether with two 20-ml. portions of water. Evaporate the ether to dryness, and dry the residue at 80° for 30 minutes: the infrared absorption spectrum of a mineral oil dispersion prepared from the residue exhibits maxima at the same wavelengths as that of NF Thiopropazate Hydrochloride Reference Standard, similarly treated and measured.

Disintegration, page 878—The disintegration time limit for Thiopropazate Hydrochloride Tablets is 15 minutes.

Content uniformity, *Method II*, page 799—Thiopropazate Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Finely powder one Thiopropazate Hydrochloride Tablet, and quantitatively transfer it to a 100-ml. volumetric flask, add 50 ml. of methanol, and allow to stand for 15 minutes. Dilute to volume with methanol, mix, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise with methanol to provide a solution containing approximately 10 mcg. per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Thiopropazate Hydrochloride Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 255 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_{23}H_{28}ClN_3O_2S.2HCl$ in the tablet by the formula $(T/D) \times C\ (A_U/A_S)$, in which T is the labeled quantity, in mg., of thiopropazate hydrochloride in the tablet; D is the exact concentration, in mcg. per ml., of thiopropazate hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Thiopropazate Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 30 mg. of thiopropazate hydrochloride, to a separator, add 20 ml. of water and 10 drops of ammonia T.S., and extract with eight 20-ml. portions of chloroform. Evaporate the chloroform to dryness on a steam bath, dissolve the residue in 25 ml. of glacial acetic acid, and titrate with 0.01 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically by means of suitable electrodes. Each ml. of 0.01 *N* perchloric acid is equivalent to 2.595 mg. of $C_{23}H_{28}ClN_3O_2S.2HCl$.

Packaging and storage—Preserve Thiopropazate Hydrochloride Tablets in well-closed light-resistant containers.

Tablets available—Thiopropazate Hydrochloride Tablets usually available contain the following amounts of thiopropazate hydrochloride: 5 and 10 mg.

CATEGORY and DOSE—See Thiopropazate Hydrochloride.

Thrombin

Thrombin is a sterile protein substance prepared from prothrombin of bovine origin through interaction with added thromboplastin in the presence of calcium. It is capable, without the addition of other substances, of causing the clotting of whole blood, plasma, or a solution of fibrinogen. It may contain a suitable antibacterial agent. Thrombin complies with the requirements of the United States Public Health Service.

Note: Solutions of Thrombin should be used within a few hours after preparation, and are not to be injected.

Description—Thrombin is a white or grayish, amorphous substance dried from the frozen state.

Other requirements—Thrombin complies with the requirements under *Biologics*, page 781, and with the solubility, safety, sterility, potency, and other requirements of the U.S. Public Health Service.

Packaging and storage—Preserve Thrombin at a temperature between 2° and 8°, preferably at the lower limit. Dispense it in the unopened container in which it was placed by the manufacturer.

Expiration date—The expiration date for Thrombin is not more than 3 years after date of manufacture or date of issue.

Sizes available—Thrombin is usually available as follows: 1000, 5000, and 10,000 NIH units.

Category—Local hemostatic.

Application—Topically as a powder or as a solution containing 1000 units per ml.

Tolu Balsam Syrup

Tolu Balsam Tincture	**50 ml.**
Magnesium Carbonate	**10 g.**
Sucrose	**820 g.**
Purified Water, a sufficient quantity,	
To make	**1000 ml.**

Add all the tincture at once to the magnesium carbonate and 60 g. of sucrose in a mortar, and mix intimately. Gradually add 430 ml. of purified water with trituration, and filter. Dissolve the remainder of the sucrose in the clear filtrate with gentle heating, strain the syrup while warm, and add sufficient purified water through the strainer to make the product measure 1000 ml. Mix thoroughly.

Note: Tolu Balsam Syrup may be made also in the following manner:

Place the remaining 760 g. of the sucrose in a suitable percolator, the neck of which is nearly filled with loosely packed cotton, moistened after packing with a few drops of water. Pour the filtrate, obtained as directed in the formula above, upon the sucrose, and regulate the outflow to a steady drip of percolate. When all of the liquid has run through, return portions of the percolate, if necessary, to dissolve all the sucrose. Then pass enough purified water through the cotton to make the product measure 1000 ml. Mix thoroughly.

Alcohol content, page 772—Tolu Balsam Syrup contains from 2 to 4 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Tolu Balsam Syrup in tight containers, preferably at a temperature not exceeding 25°.

Category—Vehicle.

Tolu Balsam Tincture

Tolu Balsam	**200 g.**
To make	**1000 ml.**

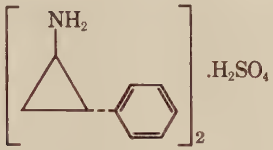
Prepare a tincture by Process M, page 838, using alcohol as the menstruum.

Alcohol content, page 772—Tolu Balsam Tincture contains from 77 to 83 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Tolu Balsam Tincture in tight, light-resistant containers, and avoid exposure to direct sunlight and to excessive heat.

Category—Flavor.

Tranylcypromine Sulfate*



(±)-*trans*-2-Phenylcyclopropylamine Sulfate (2:1)

$(C_9H_{11}N)_2.H_2SO_4$ Mol. wt. 364.47

Tranylcypromine Sulfate, dried in vacuum at 60° for 2 hours, contains not less than 98.0 percent and not more than 101.0 percent of $(C_9H_{11}N)_2.H_2SO_4$.

Description—Tranylcypromine Sulfate occurs as a white, crystalline powder. It is odorless or has a faint, cinnamaldehyde-like odor.

Solubility—Tranylcypromine Sulfate is soluble in water. It is very slightly soluble in alcohol and in ether, and is practically insoluble in chloroform.

Identification—

A: To about 10 mg. of Tranylcypromine Sulfate, add 2 ml. of alcohol and 1 ml. of ninhydrin T.S., and mix: a deep violet to purple color is observed within 5 minutes.

B: A solution of Tranylcypromine Sulfate (1 in 20) responds to the tests for *Sulfate*, page 810.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Tranylcypromine Sulfate, previously dried in vacuum at 60° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Tranylcypromine Sulfate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 2500 solution of Tranylcypromine Sulfate in dilute sulfuric acid (1 in 50) exhibits maxima and minima at the same wavelengths as that of NF Tranylcypromine Sulfate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the points of maximum absorbance occurring at about 271 mμ and at about 264 mμ, do not differ by more than 2 percent.

Loss on drying, page 814—Dry Tranylcypromine Sulfate in vacuum at 60° for 2 hours: it loses not more than 0.5 percent of its weight.

***cis*-2-Phenylcyclopropylamine sulfate**—

Standard preparation—Dissolve 10.0 mg. of NF *cis*-2-Phenylcyclopropylamine Sulfate Reference Standard, accurately weighed, in about 7 ml. of alcohol in a 10-ml. volumetric flask, add 0.2 ml. of 1 *N* sodium hydroxide, and mix. Add 2 drops of glacial acetic acid, dilute to volume with alcohol, and mix. Allow the precipitate to settle. Use the clear supernatant liquid for the test.

Test preparation—Dissolve 100.0 mg. of Tranylcypromine Sulfate, accurately weighed, in about 7 ml. of alcohol in a 10-ml. volumetric flask, add 0.2 ml. of 1 *N* sodium hydroxide, and mix. Add 2 drops of glacial acetic acid, dilute to volume with alcohol, and mix. Allow the precipitate to settle. Use the clear supernatant liquid for the test.

Procedure—Using a micropipet, apply portions of the clear *Test preparation*, each equivalent to 100 mcg. of Tranylcypromine Sulfate, to each of three points located equidistant apart on a circle of 25-mm. diameter about the center of a 33 × 57-cm. sheet of chromatographic paper. Similarly apply portions of the clear *Standard preparation*, equivalent to 1, 2, and 4 mcg. of *cis*-2-phenylcyclopropylamine sulfate, to three other points on the same circle and located midway between the *Test preparation* spots. Insert a cotton wick through a hole at the center of the circle and place the paper horizontally in a chromatographic chamber. To 50 ml. of isoamyl alcohol in a separator add 50 ml. of tertiary amyl alcohol, 100 ml. of water, and 20 ml. of formic acid, shake, and allow the layers to separate. Transfer the lower layer to the bottom of the chromatographic chamber, and allow 2 hours for equilibration. Place the upper layer of the solvent mixture in the center trough in contact with the wick, and allow the chromatogram to develop. When the solvent front has reached to within 2 cm. of the near sides of the chromatographic chamber, remove the paper and dry it in air. Spray the dried paper evenly on both sides with a solution prepared by dissolving 500 mg. of ninhydrin in 50 ml. of acetone containing 0.25 ml. of glacial acetic acid, and dry the paper for 1 hour. Calculate the R_f value for the spots obtained from each portion of the *Standard preparation*, and from the values obtained locate the spots from the *Test preparation* that correspond to the *cis*-2-phenylcyclopropylamine sulfate content: any spots produced by the sample are not more intense than that produced by the 2-mcg. *Standard preparation*, corresponding to not more than 2 percent of *cis*-2-phenylcyclopropylamine sulfate.

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* Patented. See notice, page ii.

Assay—Transfer about 1 g. of Tranylcypromine Sulfate, previously dried in vacuum at 60° for 2 hours and accurately weighed, to a 250-ml. beaker, dissolve in 75 ml. of glacial acetic acid, and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically using suitable electrodes. Each ml. of 0.1 *N* perchloric acid is equivalent to 36.45 mg. of $(C_9H_{11}N)_2 . H_2SO_4$.

Packaging and storage—Preserve Tranylcypromine Sulfate in well-closed containers.

CATEGORY—Antidepressant.

USUAL DOSE RANGE—Initial, **10 mg.** in the morning and afternoon daily for 2 weeks; if no response appears, increase dosage to **20 mg.** in the morning and **10 mg.** in the afternoon daily for another week. Maintenance, **10** to **20 mg.** per day.

Tranylcypromine Sulfate Tablets

Tranylcypromine Sulfate Tablets contain an amount of $(C_9H_{11}N)_2 . H_2SO_4$ (tranylcypromine sulfate) equivalent to not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_9H_{11}N$ (tranylcypromine).

Identification—

A: Triturate one Tranylcypromine Sulfate Tablet with 2 ml. of alcohol, add 1 ml. of ninhydrin T.S. to the suspension, and mix: a deep violet to purple color is observed within 5 minutes.

B: The solution employed for measurement of the ultraviolet absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of NF Tranylcypromine Sulfate Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Tranylcypromine Sulfate Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Tranylcypromine Sulfate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer one tablet to a 100-ml. volumetric flask, add about 50 ml. of dilute sulfuric acid (1 in 50), and shake mechanically until the tablet is completely disintegrated. Dilute to volume with dilute sulfuric acid (1 in 50), mix well, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with dilute sulfuric acid (1 in 50) to provide a solution containing tranylcypromine sulfate equivalent to approximately 80 mcg. of tranylcypromine per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Tranylcypromine Sulfate Reference Standard, in the same medium, at a concentration of about 100 mcg. per ml., in 5-cm. cells, at 285 mμ and at the maximum at about 271 mμ, with a suitable spectrophotometer, using dilute sulfuric acid (1 in 50) as the blank. Calculate the quantity, in mg., of $C_9H_{11}N$ (tranylcypromine) in the tablet by the formula $(T/D) \times (0.7309C) \times (A_{U271} - A_{U285})/(A_{S271} - A_{S285})$, in which T is the labeled quantity, in mg., of tranylcypromine in the tablet; D is the exact concentration, in mcg. per ml., of tranylcypromine in the sample solution based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; 0.7309 is the factor converting tranylcypromine sulfate to tranylcypromine, A_{U271} and A_{U285} are the absorbances of the sample solution at 271 mμ and 285 mμ, respectively, and A_{S271} and A_{S285} are the absorbances of the Reference Standard solution.

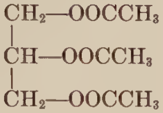
Assay—Weigh and finely powder not less than 20 Tranylcypromine Sulfate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 150 mg. of tranylcypromine, to a 250-ml. volumetric flask, add 150 ml. of water, and shake mechanically for 15 minutes. Dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate. Transfer 25.0 ml. of the subsequent filtrate to a 250-ml. separator, add 5 ml. of sodium carbonate solution (1 in 20), and extract with four 40-ml. portions of ether. Wash the combined ether extracts with 5 ml. of water, discarding the water wash. Extract the combined ether extracts with four 40-ml. portions of dilute sulfuric acid (1 in 50), collecting the acid extracts in a 200-ml. volumetric flask. Aerate to remove residual ether, dilute to volume with dilute sulfuric acid (1 in 50), and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Tranylcypromine Sulfate Reference Standard, in the same medium, at a concentration of about 100 mcg. per ml., in 5-cm. cells, at 285 mμ and at the maximum at about 271 mμ, with a suitable spectrophotometer, using dilute sulfuric acid (1 in 50) as the blank. Calculate the quantity, in mg., of $C_9H_{11}N$ (tranylcypromine) in the portion of the Tablets taken by the formula $2C \times 0.7309 \times (A_{U271} - A_{U285})/(A_{S271} - A_{S285})$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, 0.7309 is the factor converting tranylcypromine sulfate to tranylcypromine, A_{U271} and A_{U285} are the absorbances of the sample solution at 271 mμ and 285 mμ, respectively, and A_{S271} and A_{S285} are the absorbances of the Reference Standard solution.

Packaging and storage—Preserve Tranylcypromine Sulfate Tablets in well-closed, light-resistant containers.

Tablets available—Tranylcypromine Sulfate Tablets usually available contain tranylcypromine sulfate equivalent to the following amount of tranylcypromine: 10 mg.

CATEGORY and DOSE—See Tranylcypromine Sulfate.

Triacetin*



$$\begin{array}{l} CH_2\text{—}OOCCH_3 \\ | \\ CH\text{—}OOCCH_3 \\ | \\ CH_2\text{—}OOCCH_3 \end{array}$$

Glyceryl Triacetate

$C_9H_{14}O_6$ Mol. wt. 218.21

Triacetin contains not less than 97.0 percent and not more than 100.5 percent of $C_9H_{14}O_6$, calculated on the anhydrous basis.

Description—Triacetin occurs as a colorless, somewhat oily liquid having a slight, fatty odor and a bitter taste.

Solubility—Triacetin is soluble in water. It is miscible with alcohol, with ether, and with chloroform, and it is slightly soluble in carbon disulfide.

Identification—

A: Heat a few drops of Triacetin in a test tube with about 500 mg. of potassium bisulfate: pungent vapors of acrolein are evolved.

B: The solution resulting from the *Assay* responds to the tests for *Acetate*, page 807.

Specific gravity, page 866—The specific gravity of Triacetin is not less than 1.152 and not more than 1.158.

Distilling range, page 782—Not less than 95 percent of Triacetin distils between 257° and 260°.

Infrared absorption, page 866—The infrared absorption spectrum of a 1 in 100 carbon disulfide solution of Triacetin, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Triacetin Reference Standard, similarly measured.

Refractive index, page 858—The refractive index of Triacetin is not less than 1.429 and not more than 1.430.

Acidity—Dilute 25 g. of Triacetin, accurately weighed, with 50 ml. of neutralized alcohol, add 5 drops of phenolphthalein T.S., and titrate with 0.02 *N* sodium hydroxide: not more than 1.0 ml. of 0.02 *N* sodium hydroxide is required for neutralization.

Water, page 900—Determine the water content of Triacetin by the titrimetric method: not more than 0.2 percent is found.

Assay—Transfer about 1 g. of Triacetin, accurately weighed, to a 250-ml. boiling flask, add 50.0 ml. of 0.5 *N* alcoholic potassium hydroxide, connect the flask to a water-jacketed condenser, and reflux on a steam bath for 45 minutes, swirling frequently. Cool, add 5 drops of phenolphthalein T.S., and titrate the excess alkali with 0.5 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.5 *N* alcoholic potassium hydroxide is equivalent to 36.37 mg. of $C_9H_{14}O_6$.

Packaging and storage—Preserve Triacetin in tight containers, and avoid contact with metal.

CATEGORY—Local antifungal.

FOR EXTERNAL USE—Topically to affected area twice daily as a 15 percent aerosol, a 25 percent cream, or a 33 percent powder.

Triacetin Aerosol

Triacetin Aerosol is a solution of triacetin in fluorochlorohydrocarbon propellants in a pressurized container. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{14}O_6$.

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* Patented. See notice, page ii.

Identification—Spray Triacetin Aerosol into a 30-ml. beaker until about 2 ml. of liquid is collected, place the beaker on a steam bath, and heat for 1 hour. From the residue of triacetin so obtained, prepare a 1 in 100 solution in carbon disulfide. Wash 8 ml. of the solution with 2 ml. of water, discard the washing, and filter the carbon disulfide solution: the infrared absorption spectrum of the filtrate exhibits maxima at the same wavelengths as that of a 1 in 100 solution of NF Triacetin Reference Standard in carbon disulfide, similarly measured.

Other requirements—Triacetin Aerosol meets the requirements for *Leak Testing* and *Pressure Testing* under *Aerosols,* page 770.

Assay—Remove the cap, nozzle, and any paper labeling from a Triacetin Aerosol container, and weigh accurately. Store the container at −20° for at least 60 minutes, and then carefully puncture two opposing positions on the shoulder of the container. (*Caution:* Do not agitate the container contents during the puncturing.) Quickly invert the container in a 1000-ml. beaker, and allow to drain completely. Rinse the container interior with alcohol, collecting the rinsings in the beaker, dry the container in air, and weigh. Calculate the net weight, in g., of the contents of the container, and record as W. Allow the liquid in the beaker to warm to room temperature, stirring gently to hasten the evaporation of the volatile propellants, and then heat gently on a steam bath for 1 hour. Transfer the residual liquid to a 100-ml. volumetric flask with the aid of alcohol, dilute to volume with alcohol, and mix. Transfer 5.0 ml. of this solution to a 250-ml. boiling flask, and continue as directed in the *Assay* under *Triacetin,* page 713, beginning with ". . . add 50.0 ml. of 0.5 N alcoholic potassium hydroxide . . . ." Calculate the quantity, in mg., of $C_9H_{14}O_6$ in each g. of the Aerosol contents by the formula $36.37\ V \times N \times (20/W)$, in which V is the volume, in ml., and N is the exact normality of the alcoholic potassium hydroxide solution consumed.

Packaging and storage—Preserve Triacetin Aerosol in pressurized containers, and protect from excessive heat.

Aerosol available—Triacetin Aerosol usually available contains 150 mg. of triacetin per g. in 85-g. containers.

CATEGORY and APPLICATION—See Triacetin.

Triacetin Cream

Triacetin Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{14}O_6$.

Identification—Transfer a portion of Triacetin Cream, equivalent to about 2.5 g. of triacetin, to a separator, extract with 50 ml. of ether, and centrifuge for 5 minutes. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 5 µl. of the clear supernatant ether solution and 5 µl. of an ether solution of NF Triacetin Reference Standard containing 50 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of benzene and ethyl acetate (9:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Expose the plate to iodine vapors, in a suitable chamber, until spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Weight variation, page 901—Triacetin Cream meets the requirements of the weight variation test for creams.

Assay—Transfer an accurately weighed portion of Triacetin Cream, equivalent to about 1 g. of triacetin, to a 250-ml. boiling flask, and continue as directed in the *Assay* under *Triacetin,* page 713, beginning with " . . . add 50.0 ml. of 0.5 N alcoholic potassium hydroxide . . . ."

Packaging and storage—Preserve Triacetin Cream in collapsible tubes, or in tight containers.

Cream available—Triacetin Cream usually available contains 25 percent of triacetin.

CATEGORY and APPLICATION—See Triacetin.

Triacetin Powder

Triacetin Powder contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{14}O_6$ in a suitable powder base.

Identification—Triturate a portion of Triacetin Powder, equivalent to about 2.5 g. of triacetin, with 50 ml. of ether, and filter. A 5-µl. portion of the filtrate responds to the *Identification test* under *Triacetin Cream*, page 714.

Weight variation, page 901—Triacetin Powder meets the requirements of the weight variation test for powders.

Assay—Transfer an accurately weighed portion of Triacetin Powder, equivalent to about 1 g. of triacetin, to a 123 × 43-mm. (inside diameter) extraction thimble, place the thimble in a continuous-extraction apparatus, and extract with 250 ml. of ether for 4 hours, collecting the extract in a 500-ml. flask. Evaporate the ether to dryness, and continue as directed in the *Assay* under *Triacetin*, page 713, beginning with ". . . add 50.0 ml. of 0.5 *N* alcoholic potassium hydroxide. . . ."

Packaging and storage—Preserve Triacetin Powder in well-closed containers.

Powder available—Triacetin Powder usually available contains 33.3 percent of triacetin.

CATEGORY and APPLICATION—See Triacetin.

Triamcinolone Acetonide Aerosol*

Triamcinolone Acetonide Aerosol is a solution of triamcinolone acetonide in fluorochlorohydrocarbon propellants in a pressurized container. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{24}H_{31}FO_6$.

Identification—Transfer 15.0 ml. of the *Assay preparation*, prepared from Triamcinolone Acetonide Aerosol as directed in the *Assay*, to a beaker, evaporate to dryness on a steam bath with the aid of a current of air, and dissolve the residue in 1.0 ml. of methanol. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a methanol solution of NF Triamcinolone Acetonide Reference Standard containing 500 mcg. per ml. Allow the spots to dry, and develop the chromatogram, using ether as the solvent, until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 3) and drying at 100° for 15 minutes: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Other requirements—Triamcinolone Acetonide Aerosol meets the requirements for *Leak Testing* and *Pressure Testing* under *Aerosols*, page 770.

Assay—

Standard preparation—Dissolve a suitable quantity of NF Triamcinolone Acetonide Reference Standard, accurately weighed, in alcohol to yield a solution containing approximately 35 mcg. per ml.

Assay preparation—Fit the valve of a Triamcinolone Acetonide Aerosol container with a suitable tube assembly so that the contents can be sprayed directly into the bulb portion of a 50-ml. volumetric flask, and then spray about 25 g. of the contents into the flask, determining the exact amount sprayed by difference. Evaporate to dryness on a steam bath with the aid of a stream of air. Dissolve the residue in alcohol, dilute to volume with alcohol, and mix.

Procedure—Transfer 5.0 ml. each of the *Standard preparation*, of the *Assay preparation*, and of alcohol, to serve as the blank, into separate 25-ml. volumetric flasks. To each flask add 0.7 ml. of blue tetrazolium T.S. and 1.0 ml. of dilute (3 in 100 with alcohol) tetramethylammonium hydroxide T.S. Mix, allow to stand in the dark for about 60 minutes, then add to each flask 2.0 ml. of alcohol followed by 1.0 ml. of 0.1 *N* hydrochloric acid in alcohol, and mix. Dilute each flask to volume with chloroform, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 525 mµ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the weight, in mg., of $C_{24}H_{31}FO_6$ in the portion of Aerosol taken by the formula $0.05C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation.*

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* Patented. See notice, page ii.

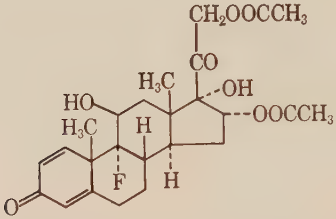
Packaging and storage—Preserve Triamcinolone Acetonide Aerosol in pressurized containers, and protect from excessive heat.

Aerosols available—Triamcinolone Acetonide Aerosol usually available contains 66 mcg. of triamcinolone acetonide per g. in 50 and 150-g. containers.

CATEGORY—Anti-inflammatory.

APPLICATION—Topically to the affected area from one to three times a day.

Triamcinolone Diacetate*



9-Fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,21-Diacetate

$C_{25}H_{31}FO_8$ Mol. wt. 478.52

Triamcinolone Diacetate contains not less than 97.0 percent and not more than 103.0 percent of $C_{25}H_{31}FO_8$, calculated on the dried basis.

Description—Triamcinolone Diacetate occurs as a fine, white to off-white, crystalline powder, possessing not more than a slight odor.

Solubility—Triamcinolone Diacetate is practically insoluble in water, slightly soluble in ether, sparingly soluble in alcohol and in methanol, and soluble in chloroform.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Triamcinolone Diacetate, previously dried in vacuum at 60° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Triamcinolone Diacetate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Triamcinolone Diacetate in dehydrated alcohol exhibits maxima and minima at the same wavelengths as that of NF Triamcinolone Diacetate Reference Standard, similarly measured, and the respective absorptivities calculated on the dried basis, at the point of maximum absorbance occurring at about 238 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Triamcinolone Diacetate in vacuum at 60° for 3 hours: it loses not more than 6 percent of its weight.

Residue on ignition, page 858—Triamcinolone Diacetate yields not more than 0.5 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Triamcinolone Diacetate is 25 parts per million.

Foreign steroids and other impurities—

Standard preparation—Prepare as directed under *Steroid Chromatographic Purity*, page 876, using NF Triamcinolone Diacetate Reference Standard, previously dried in vacuum at 60° for 3 hours.

Test preparation—Weigh accurately about 80 mg. of Triamcinolone Diacetate, previously dried in vacuum at 60° for 3 hours, dissolve it in a sufficient quantity of a mixture of equal volumes of alcohol and chloroform to make 10.0 ml., and mix.

Procedure—Proceed as directed for *Procedure* under *Steroid Chromatographic Purity*, page 876, using a solvent system consisting of benzene and isopropanol (4:1), and determining the absorbance at the maximum at about 238 mμ. Calculate the percentage of chromatographic impurities by the formula $100 - [100 \times 10 \times (C/W) \times (A_U/A_S)]$, in which C is the exact concentration, in mg. per ml., of the *Standard preparation*, and W is the weight, in mg., of Triamcinolone Diacetate taken: not more than 3 percent is found.

Assay—

Standard preparation—Prepare as directed for *Standard preparation* under *Steroid assay*, page 876, using NF Triamcinolone Diacetate Reference Standard.

Assay preparation—Weigh accurately about 100 mg. of Triamcinolone Diacetate, dissolve it in sufficient alcohol to make 200.0 ml., and mix. Transfer 5.0 ml. of this solution to a 250-ml. volumetric flask, add alcohol to volume, and mix.

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* Patented. See notice, page ii.

Transfer 20.0 ml. of this solution to a glass-stoppered, 50-ml. conical flask.

Procedure—Proceed as directed for *Procedure* under *Steroid Assay,* page 876. Calculate the quantity, in mg., of $C_{25}H_{31}FO_8$ in the portion of Triamcinolone Diacetate taken by the formula $10C \times (Av/As)$.

Packaging and storage—Preserve Triamcinolone Diacetate in well-closed containers.

CATEGORY—Glucocorticoid.
USUAL DOSE—**4 mg.** daily.
USUAL DOSE RANGE—**4** to **30 mg.** daily.

Sterile Triamcinolone Diacetate Suspension

Sterile Triamcinolone Diacetate Suspension is a sterile suspension of triamcinolone diacetate in a suitable aqueous medium. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{25}H_{31}FO_8$.

Identification—Filter a volume of Sterile Triamcinolone Diacetate Suspension, equivalent to about 200 mg. of triamcinolone diacetate, through a medium-porosity sintered-glass funnel, wash well with water, and dry the crystals in a vacuum. Dissolve 2 mg. of the dried crystals in 1 ml. of methanol in a small mortar. Evaporate to dryness using gentle heat and a stream of nitrogen: a potassium bromide dispersion of the crystals so obtained meets the requirements for *Infrared absorption* under *Triamcinolone Diacetate,* page 716.

pH, page 824—The pH of Sterile Triamcinolone Diacetate Suspension is between 5.0 and 7.0.

Other requirements—Sterile Triamcinolone Diacetate Suspension meets the requirements under *Injections,* page 810.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay,* page 876, using NF Triamcinolone Diacetate Reference Standard.

Assay preparation—Transfer to a separator an accurately measured volume of Sterile Triamcinolone Diacetate Suspension, equivalent to about 100 mg. of triamcinolone diacetate, and add 20 ml. of water. Extract with four 35-ml. portions of chloroform, filtering each portion through chloroform-washed cotton into a 250-ml. volumetric flask. Add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a 200-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this solution to a 50-ml. glass-stoppered, conical flask, evaporate the chloroform on a steam bath just to dryness, cool, and dissolve the residue in 20.0 ml. of alcohol.

Procedure—Proceed as directed under *Steroid Assay,* page 876. Calculate the quantity, in mg., of $C_{25}H_{31}FO_8$ in each ml. of the Suspension taken by the formula $10 \times (C/V) \times (Av/As)$, in which V is the volume, in ml., of the Suspension taken.

Packaging and storage—Preserve Sterile Triamcinolone Diacetate Suspension in single-dose or in multiple-dose containers, preferably of Type I glass.

Suspensions available—Sterile Triamcinolone Diacetate Suspension usually available contains the following amounts of triamcinolone diacetate: 40 mg. in 1 ml., 125 mg. in 5 ml., and 200 mg. in 5 ml.

CATEGORY and DOSE—See Triamcinolone Diacetate.

Triamcinolone Diacetate Syrup

Triamcinolone Diacetate Syrup contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{25}H_{31}FO_8$. It contains a suitable preservative.

Identification—Transfer a quantity of Triamcinolone Diacetate Syrup, equivalent to about 10 mg. of triamcinolone diacetate, to a separator, and extract with three 10-ml. portions of chloroform. Evaporate the combined chloroform extracts to dryness on a steam bath, and dissolve the residue in 5.0 ml. of chloroform. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a chloroform solution of NF Triamcinolone Diacetate Reference Standard containing 2 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of ethyl acetate and chloroform (9:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Assay—

Standard preparation—Prepare as directed under *Steroid Assay*, page 876, using NF Triamcinolone Diacetate Reference Standard.

Assay preparation—Transfer an accurately measured volume of Triamcinolone Diacetate Syrup, equivalent to about 2 mg. of triamcinolone diacetate, to a separator, and add 10 ml. of water and 5 ml. of sodium sulfate solution (1 in 20). Extract with four 25-ml. portions of chloroform, filtering each extract through chloroform-washed cotton into a 200-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer 20.0 ml. of this solution to a glass-stoppered 50-ml. conical flask, evaporate the chloroform on a steam bath just to dryness, cool, and dissolve the residue in 20.0 ml. of alcohol.

Procedure—Proceed as directed under *Steroid Assay*, page 876. Calculate the quantity, in mg., of $C_{25}H_{31}FO_8$ in each ml. of the Syrup taken by the formula $0.2 \times (C/V) \times (Au/As)$, in which V is the volume, in ml., of Syrup taken.

Packaging and storage—Preserve Triamcinolone Diacetate Syrup in tight, light-resistant containers.

Syrups available—Triamcinolone Diacetate Syrup usually available contains the following amounts of triamcinolone diacetate: 2 mg. in 5 ml., and 5 mg. in 5 ml.

CATEGORY and DOSE—See Triamcinolone Diacetate.

Tribasic Calcium Phosphate, page 127

Tribromoethanol

CBr_3CH_2OH

2,2,2-Tribromoethanol

$C_2H_3Br_3O$ Mol. wt. 282.76

Tribromoethanol contains not less than 99.0 percent and not more than 101.8 percent of $C_2H_3Br_3O$, calculated on the dried basis.

Description—Tribromoethanol occurs as a white, crystalline powder, having a slight, aromatic odor and taste. It is unstable in air and in light. Both water and alcohol solutions of Tribromoethanol decompose on exposure to light.

Solubility—Tribromoethanol is sparingly soluble in water. It is very soluble in amylene hydrate.

Identification—Dissolve about 200 mg. of Tribromoethanol in 10 ml. of water, add 1 ml. of sodium hydroxide T.S., and heat at about 100° for 30 minutes, adding water as necessary to maintain the volume. Acidify the solution slightly with nitric acid, and add a few drops of silver nitrate T.S.: a yellowish, curdy precipitate, which is insoluble in nitric acid, but soluble in an excess of stronger ammonia water, is formed.

Melting range, page 814—Tribromoethanol melts between 79° and 82°.

Acidity—A solution of Tribromoethanol (1 in 50), prepared at 35° to 40° and tested immediately, is not acid to methyl red T.S.

Loss on drying, page 814—Dry Tribromoethanol over silica gel for 4 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Tribromoethanol yields not more than 0.1 percent of residue on ignition.

Halide—Dissolve 200 mg. of Tribromoethanol in 10 ml. of water at about 40°, quickly cool to 25°, and add 5 drops of diluted nitric acid and 0.5 ml. of silver nitrate T.S.: no opalescence is produced immediately.

Readily carbonizable substances, page 856—Dissolve 100 mg. of Tribromoethanol in 1 ml. of sulfuric acid T.S.: the solution has no more color than Matching Fluid A.

Aldehyde—Dissolve 100 mg. of Tribromoethanol in 5 ml. of water at 35° to 40°, quickly cool to 25°, and add 1 ml. of phenylhydrazine acetate T.S.: no precipitate is formed within 30 minutes.

Assay—Dissolve about 300 mg. of Tribromoethanol, accurately weighed, in 20 ml. of sodium hydroxide T.S., and reflux gently for 1 hour. Rinse the reflux condenser with 20 ml. of water, cool to room temperature, add 20 ml. of diluted nitric acid, 50.0 ml. of 0.1 N silver nitrate, and

5 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Perform a blank determination (see *Residual Titrations,* page 883). Each ml. of 0.1 *N* silver nitrate is equivalent to 9.426 mg. of $C_2H_3Br_3O$.

Packaging and storage—Preserve Tribromoethanol in tight, light-resistant containers.

CATEGORY—General anesthetic.

USUAL DOSE—Rectal, **60 to 80 mg.** per kg. of body weight, not to exceed **8 g.** for woman, **10 g.** for man.

Tribromoethanol Solution

Tribromoethanol Solution is a solution of tribromoethanol in amylene hydrate. It contains, in each 100 ml., not less than 95.0 g. and not more than 105.0 g. of $C_2H_3Br_3O$.

Tribromoethanol	**100 g.**
Amylene Hydrate, a sufficient quantity,	
To make	**100 ml.**

Dissolve the tribromoethanol in 50 ml. of amylene hydrate, and add sufficient amylene hydrate to make 100 ml.

NOTE: For administration of the Solution as an anesthetic, dilute the Tribromoethanol Solution, just before use, with warm purified water in the proportion of 2.5 ml. of Solution to 100 ml. of the dilution. The diluted Tribromoethanol Solution, placed in a glass-stoppered flask at 40°, conforms to the test for *Acidity,* when treated as directed, beginning with "Shake the mixture . . . ."

Description—Tribromoethanol Solution is a clear, colorless liquid, having a camphor-like odor and a burning taste.

Acidity—Pipet 1.0 ml. of Tribromoethanol Solution into 40 ml. of water in a glass-stoppered flask at 40°. Shake the mixture until all globules have disappeared. Immediately transfer 5 ml. of the resulting solution to a test tube, and add 1 drop of congo red solution (1 in 1000): the color produced is the same as that produced by the addition of 1 drop of the congo red solution to 5 ml. of water in a similar test tube.

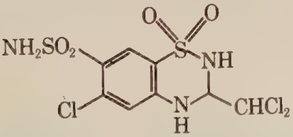
Assay—Place in a flask about 3 g. of Tribromoethanol Solution, accurately weighed, add 50 ml. of sodium hydroxide T.S., and reflux on a steam bath for 1 hour. Rinse the reflux condenser with 20 ml. of water, and add 50 ml. of diluted nitric acid. Cool the solution, transfer to a 200-ml. volumetric flask, rinse the flask with three 10-ml. portions of water, adding the rinsings to the solution, add water to volume, and mix. Pipet 25.0 ml. of the solution into a conical flask, add 50.0 ml. of 0.1 *N* silver nitrate, 5 ml. of nitric acid, and 5 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Perform a blank determination (see *Residual Titrations,* page 883).

Determine the specific gravity of Tribromoethanol Solution to the third decimal place (see page 866), and, from the value obtained, calculate the volume, to the nearest 0.01 ml. represented by the weight of Solution taken. Each ml. of 0.1 *N* silver nitrate is equivalent to 9.426 mg. of $C_2H_3Br_3O$.

Packaging and storage—Preserve Tribromoethanol Solution in tight, light-resistant containers, carefully dried prior to filling.

CATEGORY and DOSE—See Tribromoethanol.

Trichlormethiazide*



6-Chloro-3-(dichloromethyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide

$C_8H_8Cl_3N_3O_4S_2$ Mol. wt. 380.66

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* Patented. See notice, page ii.

Trichlormethiazide, dried at 105° for 3 hours, contains not less than 97.5 percent and not more than 102.5 percent of $C_8H_8Cl_3N_3O_4S_2$.

Description—Trichlormethiazide occurs as a white or practically white crystalline powder. It is odorless or has a slight characteristic odor. It melts at about 274° with decomposition.

Solubility—Trichlormethiazide is freely soluble in acetone and is soluble in methanol. It is very slightly soluble in ether and in water.

Identification—Prepare a solution of Trichlormethiazide in benzene-alcohol (1:1) containing 1 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 10 µl. of this solution and 10 µl. of a solution of NF Trichlormethiazide Reference Standard containing 1 mg. per ml. Allow the spots to dry, and develop the chromatogram, using ethyl acetate as the solvent, until the solvent front has moved about three-fourths of the length of the plate. Allow to dry, and locate the spots using shortwave ultraviolet light: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Trichlormethiazide, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Trichlormethiazide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Trichlormethiazide in methanol exhibits maxima and minima at the same wavelengths as that of NF Trichlormethiazide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 267 mµ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Trichlormethiazide at 105° for 3 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Trichlormethiazide yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II,* page 806—The heavy metals limit for Trichlormethiazide is 20 parts per million.

Selenium—A *Test Preparation* prepared with 200 mg. of Trichlormethiazide meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

Diazotizable substances—

Standard preparation—Prepare a solution in benzene-alcohol (1:1) containing 250 mcg. of NF 4-Amino-6-chloro-1,3-benzenedisulfonamide Reference Standard in each ml.

Test preparation—Transfer 100.0 mg. of Trichlormethiazide, accurately weighed, to a 10-ml. volumetric flask, dissolve in 1 ml. of acetone, dilute to volume with a mixture of benzene and alcohol (1:1), and mix.

Procedure—Apply 5 µl. each of the *Standard preparation* and of the *Test preparation* to a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in ethyl acetate until the solvent front has moved about 15 cm. from the origin. Remove the plate from the developing chamber, mark the solvent front, and locate the spots on the plate by spraying first with a 1 in 20 solution of sodium nitrite in 1 *N* hydrochloric acid, and then with a 1 in 1000 solution of *N*-(1-naphthyl)ethylenediamine dihydrochloride in alcohol: after 3 minutes, any spot from the *Test preparation,* occurring at the R_f value corresponding to that produced by the *Standard preparation,* is not greater in size or intensity than the spot produced by the *Standard preparation,* corresponding to not more than 2.5 percent of diazotizable substances.

Assay—Dissolve about 1 g. of Trichlormethiazide, previously dried at 105° for 3 hours and accurately weighed, in 100 ml. of dimethylformamide, add about 5 drops of phenol red T.S., and titrate immediately with 0.1 *N* tetrabutylammonium hydroxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* tetrabutylammonium hydroxide is equivalent to 38.07 mg. of $C_8H_8Cl_3N_3O_4S_2$.

Packaging and storage—Preserve Trichlormethiazide in well-closed containers.

CATEGORY—Diuretic; antihypertensive.

USUAL DOSE RANGE—Initial, **2** to **4 mg.** twice daily, then **2** to **4 mg.** once daily.

Trichlormethiazide Tablets

Trichlormethiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_8H_8Cl_3N_3O_4S_2$.

Identification—Evaporate 25 ml. of the combined ethyl acetate extracts obtained in the *Assay* to dryness on a steam bath, dissolve the residue in 1 ml. of benzene-alcohol (1:1): a 10-μl. portion of this solution meets the requirements of the *Identification test* under *Trichlormethiazide*, page 719.

Disintegration, page 878—The disintegration time limit for Trichlormethiazide Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Trichlormethiazide Tablets meet the requirements of the content uniformity test for tablets.

Assay—Weigh and finely powder not less than 20 Trichlormethiazide Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 4 mg. of trichlormethiazide, to a separator, and add 50 ml. of water. Extract with three 30-ml. portions of ethyl acetate, combine the extracts in a 100-ml. volumetric flask, add ethyl acetate to volume, and mix. Transfer 4.0 ml. of this solution to a 25-ml. volumetric flask, and evaporate to dryness on a warm water bath with the aid of a stream of nitrogen. Dissolve the residue of trichlormethiazide in methanol, dilute to volume with methanol, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trichlormethiazide Reference Standard, in the same medium, at a concentration of about 6.4 mcg. per ml., in 1-cm. cells, at the maximum at about 267 mμ, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg., of $C_8H_8Cl_3N_3O_4S_2$ in the portion of the Tablets taken by the formula $0.625C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Trichlormethiazide Tablets in tight containers.

Tablets available—Trichlormethiazide Tablets usually available contain the following amounts of trichlormethiazide: 2 and 4 mg.

CATEGORY and DOSE—See Trichlormethiazide.

Trichloromonofluoromethane

CCl_3F

Trichlorofluoromethane

CCl_3F Mol. wt. 137.37

Description—Trichloromonofluoromethane occurs as a clear, colorless gas having a faint, ethereal odor. Its vapor pressure at 25° is about 796 mm. of mercury (1 psig).

Identification—The infrared absorption spectrum of Trichloromonofluoromethane, determined in a 10-cm. cell with sodium chloride windows, at atmospheric pressure, exhibits maxima, among others, at the following wavelengths, in μ: 4.67 (*m*), 5.95 (*m*), 7.28 (*s*), 8.06 (*m*), 9.2 (*vs*), 10.7 (*vs*), 11.8 (*vs*), and 13.4 (*m*). The stronger maxima are best obtained at pressures less than 10 mm. of mercury.

Boiling temperature—Determine the boiling temperature of Trichloromonofluoromethane by the special procedure, page 772: it boils at approximately 24°.

Water—Determine the water content of Trichloromonofluoromethane by the special procedure, page 772: not more than 10 parts per million is found.

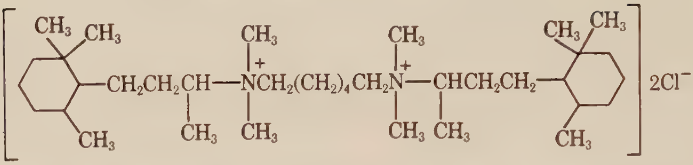
High-boiling residues—Determine the content of high-boiling residues in Trichloromonofluoromethane by the special procedure, page 772: not more than 0.01 percent is found.

Inorganic chlorides—Place 5 ml. of dehydrated methanol in a test tube, add 3 drops of a saturated solution of silver nitrate in dehydrated methanol, shake, and add 7 g. of Trichloromonofluoromethane: no opalescence or turbidity is produced.

Packaging and storage—Preserve Trichloromonofluoromethane in tight cylinders, in a cool place.

CATEGORY—Aerosol propellant.

Triclobisonium Chloride*



Hexamethylenebis[dimethyl[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-ammonium] Dichloride

$C_{36}H_{74}Cl_2N_2$ Mol. wt. 605.91

Triclobisonium Chloride contains not less than 99.0 percent and not more than 100.5 percent of $C_{36}H_{74}Cl_2N_2$, calculated on the dried basis.

Description—Triclobisonium Chloride occurs as a white or nearly white, practically odorless, crystalline powder.

Solubility—Triclobisonium Chloride is freely soluble in water, in alcohol, and in chloroform. It is practically insoluble in ether.

Identification—

A: To 5 ml. of a solution of Triclobisonium Chloride (1 in 50) add 5 ml. of ammonium reineckate T.S.: a violet precipitate is formed.

B: To 5 ml. of a solution of Triclobisonium Chloride (1 in 50) add 2 ml. of diluted nitric acid: a white precipitate is formed.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Triclobisonium Chloride, previously dried in vacuum over phosphorus pentoxide at 80° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Triclobisonium Chloride Reference Standard, similarly measured.

Loss on drying, page 814—Dry Triclobisonium Chloride in vacuum over phosphorus pentoxide at 80° for 4 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Triclobisonium Chloride yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 1 g. of Triclobisonium Chloride, accurately weighed, in a mixture of 80 ml. of glacial acetic acid and 15 ml. of mercuric acetate T.S., add 4 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 30.30 mg. of $C_{36}H_{74}Cl_2N_2$.

Packaging and storage—Preserve Triclobisonium Chloride in tight, light-resistant containers.

CATEGORY—Local anti-infective.

APPLICATION—Topically, as a 0.1 percent ointment three or four times a day; vaginal, 5 ml. of a 0.1 percent cream every night for 2 weeks.

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* Patented. See notice, page ii.

Triclobisonium Chloride Cream

Triclobisonium Chloride Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{36}H_{74}Cl_2N_2$.

Identification—Prepare a solution of Triclobisonium Chloride Cream in a mixture of chloroform, alcohol, and stronger ammonia water (4:4:1) containing the equivalent of 100 mcg. of triclobisonium chloride per ml. and filter through silicone-treated filter paper. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 10 µl. of this solution and 10 µl. of a solution of NF Triclobisonium Chloride Reference Standard, in the same medium, containing 100 mcg. per ml. Develop the chromatogram in a solvent system consisting of acetone, potassium chloride solution (1 in 20), benzene, and stronger ammonia water (80:40:5:1) until the solvent front has ascended about 15 cm. Remove the plate from the developing chamber, and allow the solvent to evaporate. Locate the spots on the plate by spraying lightly with modified Dragendorff reagent prepared as follows: dissolve 850 mg. of bismuth nitrate in a mixture of 40 ml. of water and 10 ml. of glacial acetic acid, and then prepare another solution by dissolving 8 g. of potassium iodide in 20 ml. of water; mix 5 ml. of each solution, dilute to 50 ml. with dilute sulfuric acid (1 in 10), and add 0.2 ml. of 30 percent hydrogen peroxide. The R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

pH, page 824—The pH of Triclobisonium Chloride Cream is between 3.0 and 7.0.

Weight variation, page 901—Triclobisonium Chloride Cream meets the requirements of the weight variation test for creams.

Assay—

Solvent mixture—Mix 400 ml. of chloroform with 400 ml. of alcohol and 100 ml. of stronger ammonia water.

Bromocresol green solution—Dissolve 250 mg. of bromocresol green sodium salt in 150 ml. of water, and dilute to 250 ml. with pH 5.3 phosphate buffer solution (prepared by dissolving 152 g. of monobasic sodium phosphate and 27 g. of anhydrous dibasic sodium phosphate in sufficient water to make 1000 ml., and adjusting the pH to 5.3 ± 0.1, if necessary).

Standard preparation—Weigh accurately about 75 mg. of NF Triclobisonium Chloride Reference Standard, and dissolve in sufficient *Solvent mixture* to make 250.0 ml. Dilute 10.0 ml. of this solution to 100.0 ml. with the *Solvent mixture*, and filter through silicone-treated filter paper.

Assay preparation—Transfer an accurately weighed portion of Triclobisonium Chloride Cream, equivalent to about 3 mg. of triclobisonium chloride, to a 100-ml. volumetric flask, add 50 ml. of *Solvent mixture*, and shake mechanically for 10 minutes. Dilute to volume with the *Solvent mixture*, mix, and filter through silicone-treated filter paper.

Procedure—Transfer 10.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 125-ml. separators. To each separator add 10 ml. of *Bromocresol green solution*, and mix. Extract with two 20-ml. portions of chloroform, collecting the extracts in 100-ml. volumetric flasks. Dilute to volume with chloroform, and mix. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the maximum at about 630 mμ, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{36}H_{74}Cl_2N_2$ in the portion of the Cream taken by the formula $0.1C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Triclobisonium Chloride Cream in tight, light-resistant containers.

Cream available—Triclobisonium Chloride Cream usually available contains 0.1 percent of triclobisonium chloride.

Category and Application—See Triclobisonium Chloride.

Triclobisonium Chloride Ointment

Triclobisonium Chloride Ointment contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{36}H_{74}Cl_2N_2$.

Identification—Prepare a solution of Triclobisonium Chloride Ointment in water, containing the equivalent of 100 mcg. of triclobisonium chloride per ml. Extract 10 ml. of this solution with 25 ml. of a mixture of chloroform and hexane (2:1), discard the chloroform-hexane extracts, and continue as directed in the *Identification test* under *Triclobisonium Chloride Cream*, page 772, beginning with "On a suitable thin-layer chromatographic plate . . . ."

pH, page 824—The pH of Triclobisonium Chloride Ointment is between 3.0 and 7.0.

Weight variation, page 901—Triclobisonium Chloride Ointment meets the requirements of the weight variation test for ointments.

Assay—

Aqueous solvent—Dissolve 5 g. of polyethylene glycol 4000 and 5 g. of polyethylene glycol 400 in sufficient water to make 100 ml.

Extraction solvent—Mix 300 ml. of chloroform with 200 ml. of solvent hexane.

Standard preparation—Weigh accurately about 100 mg. of NF Triclobisonium Chloride Reference Standard, and dissolve in sufficient water to make 100.0 ml.

Assay preparation—Weigh accurately a portion of Triclobisonium Chloride Ointment, equivalent to about 3 mg. of triclobisonium chloride, and dissolve in 30 ml. of water.

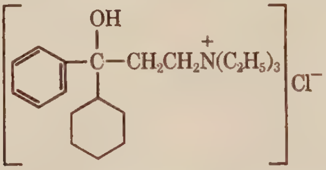
Procedure—Transfer 3.0 ml. of the *Standard preparation* into a 125-ml. separator and add 27 ml. of the *Aqueous solvent*. Transfer quantitatively the *Assay preparation* to a second 125-ml. separator. Transfer 30 ml. of the *Aqueous solvent* to a third 125-ml. separator to serve as a blank, and treat all three separators as follows: Add 50 ml. of the *Extraction solvent*, 10 ml. of bromothymol blue solution (dissolve 80 mg. of bromothymol blue in 100 ml. of 0.1 *N* sodium hydroxide), then shake the separators gently for 2 minutes and allow to stand for approximately 30 minutes. Shake the separators gently again for 2 minutes and allow the layers to separate. Collect the organic layers in 200-ml. volumetric flasks. Extract the solutions in the separators with five 25-ml. portions of the *Extraction solvent* or until the extracts are colorless, combining the extracts in the respective 200-ml. volumetric flasks. To each flask add 0.1 ml. of glacial acetic acid, mix, then dilute to volume with chloroform, and mix. Concomitantly determine the absorbances of the solutions from the *Standard preparation* and the *Assay preparation*, in 1-cm. cells, at the maximum at about 384 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{36}H_{74}Cl_2N_2$ in the portion of the Ointment taken by the formula $0.003C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Triclobisonium Chloride Ointment in tight, light-resistant containers.

Ointment available—Triclobisonium Chloride Ointment usually available contains 0.1 percent triclobisonium chloride.

CATEGORY and APPLICATION—See Triclobisonium Chloride.

Tridihexethyl Chloride*



(3-Cyclohexyl-3-hydroxy-3-phenylpropyl)triethylammonium Chloride

$C_{21}H_{36}ClNO$ Mol. wt. 353.98

Tridihexethyl Chloride, dried at 105° for 2 hours, contains not less than 98.0 percent and not more than 100.5 percent of $C_{21}H_{36}ClNO$.

Description—Tridihexethyl Chloride occurs as a white, odorless, crystalline powder.

Solubility—Tridihexethyl Chloride is freely soluble in water, in methanol, and in chloroform. It is practically insoluble in ether and in acetone.

Identification—

A: *pH 5.3 Phosphate buffer*—Dissolve 38.0 g. of monobasic sodium phosphate ($NaH_2PO_4 . H_2O$) and 2.0 g. of anhydrous dibasic sodium phosphate in water and dilute to 1000 ml.

Bromocresol purple dye solution—Dissolve 400 mg. of bromocresol purple in 30 ml. of water and 6.4 ml. of 0.1 *N* sodium hydroxide and dilute to 500 ml. with water.

Procedure—Dissolve 25 mg. of Tridihexethyl Chloride in 10 ml. of water. To 5 ml. of this solution add 2 ml. of *pH 5.3 Phosphate buffer*, 1 ml. of *Bromocresol purple dye solution*, and 5 ml. of chloroform. Mix well and allow the layers to separate: a yellow color appears in the chloroform layer.

B: The remaining 5 ml. of the solution prepared in *Identification test A* responds to the tests for *Chloride*, page 808.

C: Dissolve about 200 mg. of Tridihexethyl Chloride in 10 ml. of water, and add, with stirring, 50 ml. of sodium tetraphenylboron T.S. Allow the mixture to stand for 30 minutes, collect the precipitate on a sintered-glass filter, wash it with three 5-ml. portions of water, and draw air through the filter for 30 minutes. Dissolve the precipitate in 5 ml. of acetone, filter the solution if necessary, and pour the solution, with stirring, into 50 ml. of water. Allow the mixture to stand for 30 minutes, collect the precipitate on a sintered-glass filter, and wash it with three 5-ml. portions of water. Dry the precipitate in a vacuum desiccator over silica gel for 18 hours: the tetraphenylboron derivative so obtained melts with slight decomposition between 163° and 167°, *Class Ia*, page 815.

Melting range, page 814—Tridihexethyl Chloride melts between 196° and 202°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Tridihexethyl Chloride, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Tridihexethyl Chloride Reference Standard, similarly measured.

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* Patented. See notice, page ii.

Loss on drying, page 814—Dry Tridihexethyl Chloride at 105° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Tridihexethyl Chloride yields not more than 0.1 percent of residue on ignition.

Sulfate, page 784—Digest 500 mg. of Tridihexethyl Chloride in 25 ml. of water by heating to 70°, cool to room temperature, and filter: the filtrate shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (0.04 percent).

Chloride content—Dissolve about 500 mg. of Tridihexethyl Chloride, previously dried at 105° for 2 hours and accurately weighed, in 200 ml. of water and 10 ml. of nitric acid, add 25.0 ml. of 0.1 *N* silver nitrate, and mix. Add 5 ml. of nitrobenzene and 5 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 3.545 mg. of Cl. Not less than 9.81 percent and not more than 10.06 percent of Cl is found.

Heavy metals, *Method II*, page 806—The heavy metals limit for Tridihexethyl Chloride is 20 parts per million.

Assay—Dissolve about 600 mg. of Tridihexethyl Chloride, previously dried at 105° for 2 hours and accurately weighed, in 100 ml. of chloroform, add 5 ml. of mercuric acetate T.S. and a few crystals of thymol blue, and titrate to a pink endpoint with 0.1 *N* perchloric acid in dioxane. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 35.40 mg. of $C_{21}H_{36}ClNO$.

Packaging and storage—Preserve Tridihexethyl Chloride in tight containers.

CATEGORY—Anticholinergic.

USUAL DOSE—**25 mg.** three times a day and **50 mg.** at bedtime.

USUAL DOSE RANGE—**25** to **75 mg.** up to four times a day.

Tridihexethyl Chloride Tablets

Tridihexethyl Chloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{36}ClNO$.

Identification—

A: Finely powder a number of Tridihexethyl Chloride Tablets, equivalent to about 25 mg. of tridihexethyl chloride, add 10 ml. of water, shake, and filter: 5 ml. of the filtrate responds to *Identification test A* under *Tridihexethyl Chloride*, page 724.

B: The remaining 5 ml. of the filtrate obtained in *Identification test A* responds to the tests for *Chloride*, page 808.

Disintegration, page 878—The disintegration time limit for Tridihexethyl Chloride Tablets is 30 minutes in simulated gastric fluid T.S.

Content uniformity, *Method I*, page 799—Tridihexethyl Chloride Tablets meet the requirements of the content uniformity test for tablets.

Assay—

pH 5.3 Phosphate buffer—Prepare a pH 5.3 phosphate buffer as directed in *Identification test A* under *Tridihexethyl Chloride*, page 724.

Bromocresol purple dye solution—Prepare a bromocresol purple dye solution as directed in *Identification test A* under *Tridihexethyl Chloride*, page 724.

Standard preparation—Transfer about 100 mg. of NF Tridihexethyl Chloride Reference Standard, previously dried at 105° for 2 hours and accurately weighed, to a 100-ml. volumetric flask, dissolve in water, dilute to volume with water, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with water, and mix.

Assay preparation—Weigh and finely powder not less than 20 Tridihexethyl Chloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 25 mg. of tridihexethyl chloride, to a 250-ml. volumetric flask, add 100 ml. of water, shake, dilute to volume with water, and mix. Centrifuge a portion of this mixture.

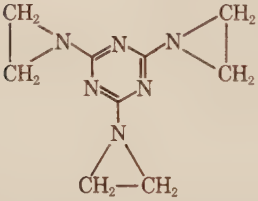
Procedure—Pipet 5.0 ml. each of the *Standard preparation* and of the *Assay preparation* into separate, 125-ml. separators. Add 5 ml. of *pH 5.3 Phosphate buffer*, 5 ml. of *Bromocresol purple dye solution*, and 10 ml. of chloroform and shake gently. Transfer the chloroform layers to separate 50-ml. volumetric flasks, and repeat the extraction of the aqueous layers with three additional 10-ml. portions of chloroform, collecting the chloroform extracts in the respective flasks. Dilute the solution in each flask to volume with chloroform, and mix. Concomitantly determine the absorbance of each solution in 1-cm. cells, at 408 mμ, with a suitable spectrophotometer, using chloroform as the blank. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{21}H_{36}ClNO$ in the portion of the Tablets taken by the formula $0.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Tridihexethyl Chloride Tablets in tight containers.

Tablets available—Tridihexethyl Chloride Tablets usually available contain the following amount of tridihexethyl chloride: 25 mg.

CATEGORY and DOSE—See Tridihexethyl Chloride.

Triethylenemelamine



2,4,6-Tris(1-aziridinyl)-*s*-triazine

$C_9H_{12}N_6$ Mol. wt. 204.24

Triethylenemelamine contains not less than 98.0 percent and not more than 100.5 percent of $C_9H_{12}N_6$, calculated on the anhydrous basis.

Caution: Triethylenemelamine is very poisonous.

Description—Triethylenemelamine occurs as a white, crystalline powder. It is odorless or has a slight, amine-like odor. It melts to a clear liquid at about 160°, and in this state polymerizes vigorously.

Solubility — Triethylenemelamine is freely soluble in water and in chloroform. It is soluble in alcohol, in acetone, in benzene, and in carbon tetrachloride.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Triethylenemelamine, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Triethylenemelamine Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 500,000 solution of Triethylenemelamine in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Triethylenemelamine Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 222 mμ, do not differ by more than 2 percent.

Water, page 900—Determine the water content of Triethylenemelamine by the titrimetric method: not more than 0.3 percent is found.

Heavy metals, page 806—Dissolve 1 g. of Triethylenemelamine in 23 ml. of water, and add 2 ml. of diluted acetic acid: the heavy metals limit for Triethylenemelamine is 50 parts per million.

Assay—Dissolve about 200 mg. of Triethylenemelamine, accurately weighed, in 50.0 ml. of sodium thiosulfate solution (1 in 5) in a glass-stoppered conical flask. Add 1 drop of methyl orange T.S., and immediately titrate with 0.1 *N* hydrochloric acid to a faint pink end-point that persists for at least 10 seconds. Stopper the flask, allow to stand for 30 minutes, then add 4 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to a faint pink end-point. Perform a blank determination with 50.0 ml. of the sodium thiosulfate solution, and subtract the volumes of 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide, respectively, from the volumes of the same solutions required with Triethylenemelamine present. Subtract the corrected volume of 0.1 *N* sodium hydroxide from the corrected volume of 0.1 *N* hydrochloric acid. Each ml. of the difference is equivalent to 6.808 mg. of $C_9H_{12}N_6$.

Packaging and storage—Preserve

Triethylenemelamine in tight, light-resistant containers, in a cold place.

Category—Antineoplastic.

Usual dose range—Initial, **2.5 mg.** daily for 2 to 3 days; maintenance, **0.5** to **1 mg.** weekly to **2.5** to **5 mg.** every 2 to 5 days.

Triethylenemelamine Tablets

Triethylenemelamine Tablets contain not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_9H_{12}N_6$.

Identification—Finely powder a number of Triethylenemelamine Tablets, equivalent to about 10 mg. of triethylenemelamine, triturate with 10 ml. of ether to a fine paste, filter, and evaporate the filtrate to dryness with the aid of a gentle stream of dry air: a potassium bromide dispersion of the residue so obtained meets the requirement for *Infrared absorption* under *Triethylenemelamine*, page 726.

Disintegration, page 878—The disintegration time limit for Triethylenemelamine Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Triethylenemelamine Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Add sufficient water to a finely powdered tablet to thoroughly wet the powder, and triturate to a smooth paste using a glass mortar and pestle. Quantitatively transfer the paste with the aid of water to a 500-ml. volumetric flask, rinsing the mortar and pestle with water and adding the rinsings to the flask. Add about 350 ml. of water, swirl for 5 minutes, then add 4 ml. of hydrochloric acid, dilute to volume with water, and mix. Filter through Whatman No. 541 or equivalent filter paper, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with 0.1 *N* hydrochloric acid to provide a solution containing approximately 5 mcg. of triethylenemelamine per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Triethylenemelamine Reference Standard, in the same medium at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 222 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_9H_{12}N_6$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of triethylenemelamine per tablet; D is the exact concentration, in mcg. per ml., of triethylenemelamine in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

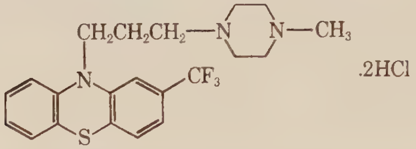
Assay—Weigh and finely powder not less than 20 Triethylenemelamine Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 25 mg. of triethylenemelamine, to a glass mortar, add enough chloroform to thoroughly wet the powder, and triturate to a paste with a glass pestle for about 4 minutes, adding chloroform as needed to keep the triturate wet. Filter the paste through a fine-porosity sintered-glass filter, washing the mortar and pestle with about 20 ml. of chloroform, and then wash the filter and filter cake with about 10 ml. of chloroform. Evaporate the extract just to dryness with the aid of a gentle stream of air (*Caution: Do not use heat!*). Dissolve the residue in 15 ml. of sodium thiosulfate solution (1 in 5), add 1 drop of methyl orange T.S., and immediately titrate with 0.1 *N* hydrochloric acid to a faint pink endpoint that persists for at least 10 seconds. Stopper the flask, allow to stand for 30 minutes, then add 4 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to a faint pink endpoint. Perform a blank determination, and subtract the volumes of 0.1 *N* hydrochloric acid and 0.1 *N* sodium hydroxide, respectively, from the volumes of the same solutions required with triethylenemelamine present. Subtract the corrected volume of 0.1 *N* sodium hydroxide from the corrected volume of 0.1 *N* hydrochloric acid. Each ml. of the difference is equivalent to 6.808 mg. of $C_9H_{12}N_6$.

Packaging and storage—Preserve Triethylenemelamine Tablets in tight containers in a refrigerator.

Tablets available—Triethylenemelamine Tablets usually available contain the following amount of triethylenemelamine: 5 mg.

Category and Dose—See Triethylenemelamine.

Trifluoperazine Hydrochloride*



10-[3-(4-Methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)phenothiazine Dihydrochloride

$C_{21}H_{24}F_3N_3S.2HCl$ Mol. wt. 480.43

Trifluoperazine Hydrochloride, dried in vacuum at 60° for 4 hours, contains not less than 98.0 percent and not more than 101.0 percent of $C_{21}H_{24}F_3N_3S.2HCl$.

Description—Trifluoperazine Hydrochloride occurs as a white to pale yellow, crystalline powder. It is practically odorless and has a bitter taste. It melts at about 242° with decomposition.

Solubility—Trifluoperazine Hydrochloride is freely soluble in water, is soluble in alcohol, and sparingly soluble in chloroform. It is insoluble in ether and benzene.

Identification—

A: A solution of Trifluoperazine Hydrochloride (1 in 100) responds to the tests for *Chloride,* page 808.

B: To 2 ml. of a solution of Trifluoperazine Hydrochloride (1 in 100) add 1 drop of ferric chloride T.S.: an amber color is produced.

C: Prepare a solution of Trifluoperazine Hydrochloride in methanol containing 1.2 mg. per ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 5 μl. of this solution and 5 μl. of a methanol solution of NF Trifluoperazine Hydrochloride Reference Standard containing 1.2 mg. per ml. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of acetone and stronger ammonia water (200:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with a solution of iodoplatinic acid prepared by dissolving 100 mg. of chloroplatinic acid in 1 ml. of 1 *N* hydrochloric acid, adding 25 ml. of potassium iodide solution (1 in 25), diluting to 100 ml. with water, and then adding 0.5 ml. of formic acid: the R_f value of the main spot from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Trifluoperazine Hydrochloride, previously dried in vacuum at 60° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Trifluoperazine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Trifluoperazine Hydrochloride in dilute hydrochloric acid (1 in 100) exhibits maxima and minima at the same wavelengths as that of NF Trifluoperazine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 255 mμ, do not differ by more than 2 percent.

pH, page 824—The pH of a solution of Trifluoperazine Hydrochloride (1 in 20) is between 1.7 and 2.6.

Loss on drying, page 814—Dry Trifluoperazine Hydrochloride in vacuum at 60° for 4 hours: it loses not more than 1.5 percent of its weight.

Residue on ignition, page 858—Trifluoperazine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 500 mg. of Trifluoperazine Hydrochloride, previously dried in vacuum at 60° for 4 hours and accurately weighed, in 50 ml. of glacial acetic acid, add 3 drops of crystal violet T.S. and 15 ml. of mercuric acetate T.S. Titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue-green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 24.02 mg. of $C_{21}H_{24}F_3N_3S.2HCl$.

Packaging and storage—Preserve Trifluoperazine Hydrochloride in tight, light-resistant containers.

CATEGORY—Tranquilizer (major).

USUAL DOSE RANGE—Oral, nonhospitalized patients—**1** to **2 mg.** twice daily; hospitalized patients—**2** to **5 mg.** daily initially, gradually increasing to the optimum level of **15** or **20 mg.** daily, although a few patients may require 40 mg. a day or more. Intramuscular, **1** to **2 mg.** every 4 to 6 hours as required.

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* Patented. See notice, page ii.

Trifluoperazine Hydrochloride Injection

Trifluoperazine Hydrochloride Injection is a sterile solution of trifluoperazine hydrochloride in water for injection. It contains an amount of $C_{21}H_{24}F_3N_3S.2HCl$ (trifluoperazine hydrochloride) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{24}F_3N_3S$ (trifluoperazine).

Identification—

A: Mix 5 ml. of Trifluoperazine Hydrochloride Injection with 5 ml. of methanol: a 5-µl. portion of this solution responds to *Identification test C* under *Trifluoperazine Hydrochloride*, page 728.

B: The solution employed for measurement of the absorbance in the *Assay* exhibits ultraviolet maxima and minima at the same wavelengths as that of NF Trifluoperazine Hydrochloride Reference Standard, similarly measured.

pH, page 824—The pH of Trifluoperazine Hydrochloride Injection is between 4.0 and 5.0.

Other requirements—Trifluoperazine Hydrochloride Injection meets the requirements under *Injections*, page 810.

Assay—[Note: Use low-actinic glassware.] Transfer an accurately measured volume of Trifluoperazine Hydrochloride Injection, equivalent to about 20 mg. of trifluoperazine, to a 250-ml. separator. Add 10 ml. of dilute sulfuric acid (1 in 10), and extract with three 25-ml. portions of carbon tetrachloride. Discard the carbon tetrachloride after each extraction. Add 10 ml. of stronger ammonia water, and extract with five 40-ml. portions of cyclohexane. Extract the combined cyclohexane extracts with five 50-ml. portions of dilute hydrochloric acid (1 in 100), collecting the aqueous extracts in a 500-ml. volumetric flask. Add dilute hydrochloric acid (1 in 100) to volume, and mix. Transfer 25.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with dilute hydrochloric acid (1 in 100), and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trifluoperazine Hydrochloride Reference Standard, in the same medium, at a concentration of about 12 mcg. per ml., in 1-cm. cells, at 278 mµ and at the maximum at about 255 mµ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{21}H_{24}F_3N_3S$ (trifluoperazine) in each ml. of the Injection taken by the formula $2 \times (C/V) \times 0.8482 \times (A_{U255} - A_{U278})/(A_{S255} - A_{S278})$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Injection taken, 0.8482 is the factor converting trifluoperazine hydrochloride to trifluoperazine, A_{U255} and A_{U278} are the absorbances of the sample solution at 255 mµ and 278 mµ, respectively, and A_{S255} and A_{S278} are the absorbances of the Reference Standard solution.

Packaging and storage—Preserve Trifluoperazine Hydrochloride Injection in multiple-dose containers, preferably of Type I glass, protected from light.

Injection available—Trifluoperazine Hydrochloride Injection usually available contains trifluoperazine hydrochloride equivalent to the following amount of trifluoperazine: 20 mg. in 10 ml.

Category and Dose—See Trifluoperazine Hydrochloride.

Trifluoperazine Hydrochloride Tablets

Trifluoperazine Hydrochloride Tablets contain an amount of $C_{21}H_{24}F_3N_3S.2HCl$ (trifluoperazine hydrochloride) equivalent to not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{21}H_{24}F_3N_3S$ (trifluoperazine).

Identification—

A: Triturate a portion of powdered Trifluoperazine Hydrochloride Tablets, equivalent to about 10 mg. of trifluoperazine, with 10 ml. of methanol, and centrifuge. A 5-µl. portion of this solution responds to *Identification test C* under *Trifluoperazine Hydrochloride*, page 728.

B: The solution employed for measurement of the absorbance in the *Assay* exhibits ultraviolet maxima and minima at the same wavelengths as that of NF Trifluoperazine Hydrochloride Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Trifluoperazine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Trifluoperazine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer one tablet to a 100-ml. volumetric flask, add about 50 ml. of dilute hydrochloric acid (1 in 100), and shake mechanically until the tablet is completely disintegrated. Dilute to volume with dilute hydrochloric acid (1 in 100), mix well, and filter, discarding the first 25 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with dilute hydrochloric acid (1 in 100) to provide a solution containing approximately 10 mcg. of trifluoperazine per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Trifluoperazine Hydrochloride Reference Standard, in the same medium, at a concentration of about 12 mcg. per ml., in 1-cm. cells, at 278 mμ and at the maximum at about 255 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{21}H_{24}F_3N_3S$ (trifluoperazine) in the tablet by the formula $(T/D) \times C \times 0.8482 \times (A_{U255} - A_{U278})/(A_{S255} - A_{S278})$, in which T is the labeled quantity, in mg., of trifluoperazine in the tablet; D is the exact concentration, in mcg. per ml., of trifluoperazine (base) in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; 0.8482 is the factor converting trifluoperazine hydrochloride to trifluoperazine; A_{U255} and A_{U278} are the absorbances of the tablet extract at 255 mμ and 278 mμ, respectively; and A_{S255} and A_{S278} are the absorbances of the Reference Standard solution.

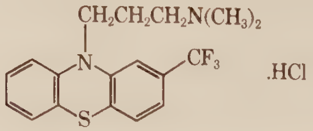
Assay—Weigh and finely powder not less than 20 Trifluoperazine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of trifluoperazine, to a 250-ml. volumetric flask, add 150 ml. of dilute hydrochloric acid (1 in 100), and shake mechanically for 15 minutes. Dilute to volume with dilute hydrochloric acid (1 in 100), mix, and filter a portion of the suspension, discarding the first 25 ml. of filtrate. Transfer 25.0 ml. of the subsequent filtrate to a 250-ml. separator, make alkaline with stronger ammonia water, and extract with four 25-ml. portions of ether. Extract the combined ether extracts with four 25-ml. portions of dilute hydrochloric acid (1 in 100), collecting the aqueous extracts in a 200-ml. volumetric flask. Aerate to remove residual ether, dilute to volume with dilute hydrochloric acid (1 in 100), and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trifluoperazine Hydrochloride Reference Standard, in the same medium, at a concentration of about 12 mcg. per ml., in 1-cm. cells, at 278 mμ and at the maximum at about 255 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{21}H_{24}F_3N_3S$ (trifluoperazine) in the portion of the Tablets taken by the formula $2C \times 0.8482 \times (A_{U255} - A_{U278})/(A_{S255} - A_{S278})$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, 0.8482 is the factor converting trifluoperazine hydrochloride to trifluoperazine, A_{U255} and A_{U278} are the absorbances of the sample solution at 255 mμ and 278 mμ, respectively, and A_{S255} and A_{S278} are the absorbances of the Reference Standard solution.

Packaging and storage—Preserve Trifluoperazine Hydrochloride Tablets in well-closed, light-resistant containers.

Tablets available—Trifluoperazine Hydrochloride Tablets usually available contain trifluoperazine hydrochloride equivalent to the following amounts of trifluoperazine: 1, 2, 5, and 10 mg.

CATEGORY and DOSE—See Trifluoperazine Hydrochloride.

Triflupromazine Hydrochloride*



10-[3-(Dimethylamino)propyl]-2-(trifluoromethyl)phenothiazine Monohydrochloride

$C_{18}H_{19}F_3N_2S \cdot HCl$ Mol. wt. 388.89

Triflupromazine Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{18}H_{19}F_3N_2S \cdot HCl$, calculated on the dried basis.

Description—Triflupromazine Hydrochloride occurs as a white to pale tan, crystalline powder, with a slight characteristic odor. It melts between 170° and 178°.

Solubility—Triflupromazine Hydrochloride is soluble in water, in alcohol, and in acetone. It is insoluble in ether.

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* Patented. See notice, page ii.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Triflupromazine Hydrochloride, previously dried at 100° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Triflupromazine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Triflupromazine Hydrochloride in 0.5 *N* sulfuric acid exhibits maxima and minima at the same wavelengths as that of NF Triflupromazine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities calculated on the dried basis, at the point of maximum absorbance occurring at about 255 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Triflupromazine Hydrochloride at 100° for 2 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Triflupromazine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Assay—Dissolve about 800 mg. of Triflupromazine Hydrochloride, accurately weighed, in 100 ml. of glacial acetic acid. Add 10 ml. of mercuric acetate T.S. and 1 drop of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 38.89 mg. of $C_{18}H_{19}F_3N_2S.HCl$.

Packaging and storage—Preserve Triflupromazine Hydrochloride in well-closed, light-resistant, glass containers.

CATEGORY—Tranquilizer (major).

USUAL DOSE RANGE—Oral, **30** to **150 mg.** daily; intramuscular, **5** to **10 mg.,** repeated in 4 hours, if necessary; intravenous, **1** to **3 mg.,** repeated in 4 hours, if necessary.

Triflupromazine Hydrochloride Tablets

Triflupromazine Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{18}H_{19}F_3N_2S.HCl$.

Identification—The solution prepared from Triflupromazine Hydrochloride Tablets for measurement of absorbance in the *Assay* exhibits an absorbance at 255 ± 2 mμ.

Disintegration, page 878—The disintegration time limit for Triflupromazine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method I*, page 799—Triflupromazine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets.

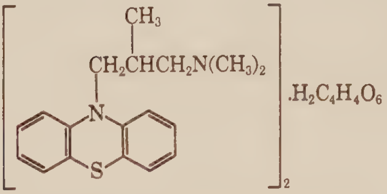
Assay—Weigh and finely powder not less than 20 Triflupromazine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of triflupromazine hydrochloride, to a separator, add 10 ml. of hydrochloric acid solution (1 in 100) and 20 ml. of water, and mix. Add sufficient ammonia T.S. to make the mixture alkaline to litmus, add 1 ml. excess, and then extract with five 50-ml. portions of chloroform, passing each extract through anhydrous sodium sulfate into a 250-ml. volumetric flask. Dilute to volume with chloroform, and mix. Evaporate 10.0 ml. of this solution to dryness under reduced pressure, and dissolve the residue in sufficient hydrochloric acid solution (1 in 100) to make 100.0 ml. Concomitantly determine the absorbance of this solution and of a solution of NF Triflupromazine Hydrochloride Reference Standard, in the same medium at a concentration of about 8 mcg. per ml., in 1-cm. cells, at the maximum at about 255 mμ, with a suitable spectrophotometer, using hydrochloric acid solution (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{18}H_{19}F_3N_2S.HCl$ in the portion of Tablets taken by the formula $6.25C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Triflupromazine Hydrochloride Tablets in well-closed, light-resistant containers.

Tablets available—Triflupromazine Hydrochloride Tablets usually available contain the following amounts of triflupromazine hydrochloride: 10, 25, and 50 mg.

CATEGORY and DOSE—See Triflupromazine Hydrochloride.

Trimeprazine Tartrate*



±-10-[3-(Dimethylamino)-2-methylpropyl]phenothiazine Tartrate (2:1)

$(C_{18}H_{22}N_2S)_2 . C_4H_6O_6$ Mol. wt. 747.00

Trimeprazine Tartrate, dried in vacuum at 60° for 4 hours, contains not less than 98.0 percent and not more than 101.0 percent of $(C_{18}H_{22}N_2S)_2 . C_4H_6O_6$.

Description—Trimeprazine Tartrate occurs as a white to off-white, odorless crystalline powder.

Solubility—Trimeprazine Tartrate is freely soluble in water and in chloroform. It is soluble in alcohol and is very slightly soluble in ether and in benzene.

Identification—

A: To 2 ml. of a solution of Trimeprazine Tartrate (1 in 100) add 1 drop of ferric chloride T.S.: a transient orange color is produced, immediately followed by a yellow precipitate.

B: Transfer 100 mg. of Trimeprazine Tartrate to a 250-ml. separator, dissolve in 50 ml. of water, make alkaline with sodium hydroxide T.S., and extract with two 50-ml. portions of ether. Acidify a 10-ml. aliquot of the aqueous layer with acetic acid, add 1 drop of ferrous sulfate T.S., 3 drops of hydrogen peroxide T.S., and an excess of sodium hydroxide T.S.: a purplish violet color is produced.

C: Prepare a solution of Trimeprazine Tartrate in methanol containing 6 mg. in each 5 ml. On a suitable thin-layer chromatographic plate (see page 791), coated with a 0.25-mm. layer of silica gel G, spot 5 µl. of this solution and 5 µl. of a methanol solution of NF Trimeprazine Tartrate Reference Standard containing 6 mg. in each 5 ml. Allow the spots to dry, and develop the chromatogram in a solvent system prepared by mixing 0.15 ml. of stronger ammonia water with 100 ml. of acetone until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with iodoplatinic acid solution [prepared by dissolving 100 mg. of chloroplatinic acid in 1 ml. of 1 *N* hydrochloric acid, adding 25 ml. of potassium iodide solution (1 in 25), diluting to 100 ml. with water, and adding 0.5 ml. of formic acid]: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Trimeprazine Tartrate, previously dried in vacuum at 60° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Trimeprazine Tartrate Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 150,000 solution of Trimeprazine Tartrate in dilute hydrochloric acid (1 in 100) exhibits maxima and minima at the same wavelengths as that of NF Trimeprazine Tartrate Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 251 mµ, do not differ by more than 2 percent.

Loss on drying, page 814—Dry Trimeprazine Tartrate in vacuum at 60° for 4 hours: it loses not more than 0.5 percent of its weight.

Assay—Dissolve about 1 g. of Trimeprazine Tartrate, previously dried in vacuum at 60° for 4 hours and accurately weighed, in a mixture of 50 ml. of chloroform and 50 ml. of glacial acetic acid, add 3 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a blue end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 37.35 mg. of $(C_{18}H_{22}N_2S)_2 . C_4H_6O_6$.

Packaging and storage—Preserve Trimeprazine Tartrate in tight, light-resistant containers.

CATEGORY—Antipruritic.

USUAL DOSE—**2.5 mg.** four times a day.

USUAL DOSE RANGE—**10** to **40 mg.** daily.

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* Patented. See notice, page ii.

Trimeprazine Tartrate Syrup

Trimeprazine Tartrate Syrup contains an amount of $(C_{18}H_{22}N_2S)_2 \cdot C_4H_6O_6$ (trimeprazine tartrate) equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{18}H_{22}N_2S$ (trimeprazine).

Identification—

A: Mix 10 ml. of Trimeprazine Tartrate Syrup and about 30 ml. of water in a separator, make the solution alkaline with sodium hydroxide T.S., and extract with two 30-ml. portions of ether. Transfer the ether extracts to a beaker, evaporate the ether by warming, and dissolve the residue in 5 ml. of methanol: 5 µl. of this solution responds to *Identification test C* under *Trimeprazine Tartrate*, page 732.

B: The solution employed for measurement of absorbance in the *Assay* exhibits ultraviolet maxima and minima at the same wavelengths as that of NF Trimeprazine Tartrate Reference Standard, similarly measured.

Assay—Transfer an accurately measured volume of Trimeprazine Tartrate Syrup, equivalent to about 2.5 mg. of trimeprazine, to a 250-ml. separator, add about 100 ml. of water and 10 ml. of sodium hydroxide solution (1 in 10), mix, and extract with four 40-ml. portions of cyclohexane. Wash the combined cyclohexane extracts with 20 ml. of water, discarding the water wash. Extract the combined cyclohexane extracts with five 40-ml. portions of dilute hydrochloric acid (1 in 100), collecting the acid extracts in a 500-ml. volumetric flask, dilute to volume with dilute hydrochloric acid (1 in 100), and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trimeprazine Tartrate Reference Standard, in the same medium at a concentration of about 6 mcg. per ml., in 1-cm. cells, at 276 mµ and at the maximum at about 251 mµ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{18}H_{22}N_2S$ (trimeprazine) in each ml. of the Syrup taken by the formula $0.5 \times (C/V) \times 0.7991 \times (A_{U251} - A_{U276})/(A_{S251} - A_{S276})$, in which C is the exact concentration in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Syrup taken, 0.7991 is the factor converting trimeprazine tartrate to trimeprazine, A_{U251} and A_{U276} are the absorbances of the sample solution at 251 mµ and 276 mµ, respectively, and A_{S251} and A_{S276} are the absorbances of the Reference Standard solution.

Alcohol content, page 772—Trimeprazine Tartrate Syrup contains from 4.5 to 6.5 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Trimeprazine Tartrate Syrup in tight, light-resistant containers.

Syrup available—Trimeprazine Tartrate Syrup usually available contains trimeprazine tartrate equivalent to the following amount of trimeprazine: 2.5 mg. in 5 ml.

CATEGORY and DOSE—See Trimeprazine Tartrate.

Trimeprazine Tartrate Tablets

Trimeprazine Tartrate Tablets contain an amount of $(C_{18}H_{22}N_2S)_2 \cdot C_4H_6O_6$ (trimeprazine tartrate) equivalent to not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{22}N_2S$ (trimeprazine).

Identification—

A: Triturate a portion of powdered Trimeprazine Tartrate Tablets, equivalent to about 10 mg. of trimeprazine, with 10 ml. of methanol and centrifuge: 5 µl. of this solution responds to *Identification test C* under *Trimeprazine Tartrate*, page 732.

B: The solution employed for measurement of absorbance in the *Assay* exhibits ultraviolet maxima and minima at the same wavelengths as that of NF Trimeprazine Tartrate Reference Standard, similarly measured.

Disintegration, page 878—The disintegration time limit for Trimeprazine Tartrate Tablets is 30 minutes.

Content uniformity, *Method II*, page 799—Trimeprazine Tartrate Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Transfer one tablet to a 100-ml. volumetric flask, add about 50 ml. of dilute hydrochloric acid (1 in 100), and shake mechanically until the tablet is completely disintegrated. Dilute to volume with dilute hydrochloric acid (1 in 100), mix well, and filter, discarding the first 20 ml. of filtrate. Dilute a portion of the subsequent filtrate, quantitatively and stepwise if necessary, with dilute hydrochloric acid (1 in 100) to provide a solution containing approximately 5 mcg. of trimeprazine per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Trimeprazine Tartrate Reference Standard, in the same medium, at a concentration of about 6 mcg. per ml., in 1-cm. cells, at 276 mμ and at the maximum at about 251 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{18}H_{22}N_2S$ (trimeprazine) in the tablet by the formula $(T/D) \times (0.7991C) \times (A_{U251} - A_{U276})/(A_{S251} - A_{S276})$, in which T is the labeled quantity, in mg., of trimeprazine in the tablet; D is the exact concentration, in mcg. per ml., of trimeprazine in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of the Reference Standard solution; 0.7991 is the factor converting trimeprazine tartrate to trimeprazine; A_{U251} and A_{U276} are the absorbances of the sample solution at 251 mμ and 276 mμ, respectively; and A_{S251} and A_{S276} are the absorbances of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Trimeprazine Tartrate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 25 mg. of trimeprazine, to a 250-ml. volumetric flask, add about 100 ml. of water and 2.5 ml. of hydrochloric acid, and shake mechanically for about 15 minutes. Dilute to volume with water, mix, and filter, discarding the first 20 ml. of filtrate. Transfer 10.0 ml. of the subsequent filtrate to a 250-ml. separator, add about 20 ml. of water, make alkaline with stronger ammonia water, and extract with four 25-ml. portions of ether. Extract the combined ether extracts with four 25-ml. portions of dilute hydrochloric acid (1 in 100), collecting the aqueous acid extracts in a 200-ml. volumetric flask. Aerate to remove residual ether, dilute to volume with dilute hydrochloric acid (1 in 100), and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trimeprazine Tartrate Reference Standard, in the same medium at a concentration of about 6 mcg. per ml., in 1-cm. cells, at 276 mμ and at the maximum at about 251 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{18}H_{22}N_2S$ (trimeprazine) in the portion of the Tablets taken by the formula $5C \times 0.7991 \times (A_{U251} - A_{U276})/(A_{S251} - A_{S276})$, in which C is the exact concentration of trimeprazine tartrate in the Reference Standard solution, in mcg. per ml.; 0.7991 is the factor converting trimeprazine tartrate to trimeprazine; A_{U251} and A_{U276} are the absorbances of the sample solution at 251 mμ and 276 mμ, respectively; and A_{S251} and A_{S276} are the absorbances of the Reference Standard solution.

Packaging and storage—Preserve Trimeprazine Tartrate Tablets in well-closed, light-resistant containers.

Tablets available—Trimeprazine Tartrate Tablets usually available contain trimeprazine tartrate equivalent to the following amount of trimeprazine: 2.5 mg.

CATEGORY and DOSE—See Trimeprazine Tartrate.

Trimethadione Tablets

Trimethadione Tablets contain not less than 94.0 percent and not more than 106.0 percent of the labeled amount of $C_6H_9NO_3$.

Identification—

A: To a portion of powdered Trimethadione Tablets, equivalent to about 1 g. of trimethadione, add 10 ml. of solvent hexane, and digest with frequent agitation for 15 minutes. Decant the solvent hexane as completely as possible, and repeat the extraction in the same manner. Transfer the residue to a stoppered flask, digest it with 25 ml. of ether for 20 minutes, decant the ether through a filter, and if an insoluble residue remains digest it with another 10-ml. portion of ether as before, and filter into the first ether filtrate. Evaporate the ether solution to dryness, preferably with a current of air, and dry the residue in a vacuum desiccator for 2 hours: the trimethadione so obtained melts between 45° and 47°, page 814.

B: To 5 ml. of a 1 in 50 solution prepared with a portion of the trimethadione obtained in *Identification test A* add 2 ml. of barium hydroxide T.S.: a precipitate is formed immediately.

C: To 500 mg. of trimethadione, obtained in *Identification test A*, add 3 ml. of sodium hydroxide solution (1 in 4), heat for 30 minutes on a steam bath, and finally evaporate to a volume of about 0.5 ml. over a free flame. Cool, cautiously acidify the residue with hydrochloric acid, using litmus paper as the indicator, and add 1 drop of ferric chloride T.S. to 10 drops of the solution so prepared: a deep yellow color is produced.

D: Place the remainder of the acid solution obtained in *Identification test C* in a separator, and extract with three 10-ml. portions of ether. Evaporate the ether on a steam bath: the residue of *N*-methyl-α-hydroxybutyramide so obtained, recrystallized from benzene and dried over phosphorus pentoxide for 4 hours, melts at about 75°, page 814.

Disintegration, page 878—The disintegration time limit for Trimethadione Tablets is 30 minutes.

Weight variation, page 901—Trimethadione Tablets meet the requirements of the weight variation test for tablets.

Assay—Weigh and finely powder not less than 20 Trimethadione Tablets. Weigh accurately a portion of the powder, equivalent to about 300 mg. of trimethadione, and digest it in a small covered beaker or flask with 10 ml. of alcohol for 10 minutes. Decant the alcohol solution through a filter into a 500-ml. Kjeldahl flask, and extract the residue with 5 ml. of alcohol in the same manner as before. Wash the beaker and the residue with a few small portions of alcohol, adding the washings to the main alcohol filtrate, add 200 ml. of water and 50 ml. of sodium hydroxide solution (2 in 5). Connect the flask by means of a distillation trap to a well-cooled condenser that dips into 40 ml. of boric acid solution (1 in 25). Boil gently for 20 minutes, avoiding as much as possible distilling any of the liquid. Then increase the temperature and distil about 200 ml. Cool the flask, add 75 ml. of water, and distil, collecting an additional 70 ml. of distillate in the same receiver. Add 3 drops of methyl red T.S., and titrate with 0.1 *N* sulfuric acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sulfuric acid is equivalent to 14.31 mg. of $C_6H_9NO_3$.

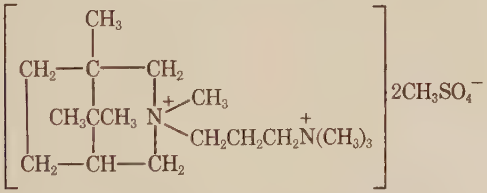
Packaging and storage—Preserve Trimethadione Tablets in tight containers, preferably at a temperature not exceeding 25°.

Tablets available—Trimethadione Tablets usually available contain the following amount of trimethadione: 150 mg.

Category—Anticonvulsant.

Usual dose of trimethadione—**300 mg.** three times a day.

Trimethidinium Methosulfate*



1,3,8,8-Tetramethyl-3-[3-(trimethylammonio)propyl]-3-azoniabicyclo[3.2.1]octane Bis(methyl sulfate)

$C_{19}H_{42}N_2O_8S_2$ Mol. wt. 490.68

Trimethidinium Methosulfate contains not less than 97.0 percent and not more than 102.0 percent of $C_{19}H_{42}N_2O_8S_2$, calculated on the anhydrous basis.

Description—Trimethidinium Methosulfate occurs as a white, hygroscopic powder. It may have a slight camphoraceous odor.

Solubility—Trimethidinium Methosulfate is very soluble in water and in alcohol, very slightly soluble in acetone, and insoluble in ether.

Identification—

A: Mix a 1 in 50 solution of Trimethidinium Methosulfate with an equal volume of picric acid T.S. Remove the precipitate by filtration, wash first with water then with ether, and air-dry: the crystals so obtained melt between 303° and 305°, page 814. (*Caution: Picrates may be explosive.*)

B: The chloroplatinate obtained in the *Assay* melts between 263° and 265°, page 814.

C: Dissolve 100 mg. of the Trimethidinium Methosulfate in 2 ml. of hydrochloric acid, heat to boiling, cool, and add 1 drop of barium chloride T.S.: a white precipitate is formed.

Melting range, page 814—Trimethidinium Methosulfate melts within a 3° range between 194° and 202°.

pH, page 824—The pH of a solution of Trimethidinium Methosulfate (1 in 50) is between 4.0 and 6.5.

Water—Determine the water content of Trimethidinium Methosulfate by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Trimethidinium Methosulfate yields not more than 0.1 percent of residue on ignition.

Selenium—A *Test Preparation* prepared with 200 mg. of Trimethidinium Methosulfate meets the requirements of the *Selenium Limit Test,* page 865 (30 parts per million).

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* Patented. See notice, page ii.

Dimethyl sulfate—Dissolve 10 g. of Trimethidinium Methosulfate in 50 ml. of water in a separator, and extract with four 25-ml. portions of ether, collecting the extracts in a second separator. Wash the combined extracts with two 10-ml. portions of water, discard the washings, and evaporate the solution just to dryness on a steam bath. Dissolve the residue in 10 ml. of sodium hydroxide solution (1 in 100), and heat on a steam bath for 30 minutes. Cool, add diluted hydrochloric acid until slightly acid, filter if necessary, and add 1 ml. of barium chloride T.S.: any opalescence developing in 5 minutes is not greater than that produced in a control containing 0.1 ml. of 0.02 *N* sulfuric acid diluted with water to a volume corresponding to the final volume in the treatment of the sample (10 parts per million as SO_4).

Assay—Dissolve about 40 mg. of Trimethidinium Methosulfate, accurately weighed, in 30 ml. of water, add 5 ml. of chloroplatinic acid solution (1 in 10), mix well, and cool in an ice bath for about 3 hours. Collect the precipitate on a tared, fine-porosity sintered-glass weighing funnel, completing the transfer using the cold filtrate. Wash with two 5-ml. portions of cold water, followed by 50 ml. of ether. Dry the precipitate to constant weight at 105°, cool, and weigh. The weight of the chloroplatinate so obtained, multiplied by 0.7232, represents its equivalent of $C_{19}H_{42}N_2O_8S_2$.

Packaging and storage—Preserve Trimethidinium Methosulfate in tight containers.

CATEGORY—Antihypertensive.

USUAL DOSE—Initial, **20 mg.** two times a day, increasing by 20-mg. increments every third day until the desired response is obtained.

USUAL DOSE RANGE—**40 mg.** to **300 mg.** daily in divided doses.

Trimethidinium Methosulfate Tablets

Trimethidinium Methosulfate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{19}H_{42}N_2O_8S_2$.

Identification—The chloroplatinate obtained in the *Assay* melts between 263° and 265°, page 814.

Disintegration, page 878—The disintegration time limit for Trimethidinium Methosulfate Tablets, using simulated gastric fluid T.S. as the test medium in place of water, is 15 minutes.

Content uniformity, *Method I*, page 799—Trimethidinium Methosulfate Tablets meet the requirements of the content uniformity test for tablets.

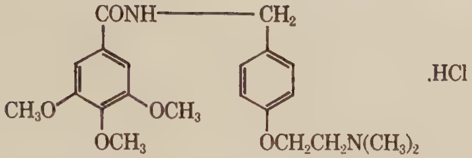
Assay—Weigh and finely powder not less than 20 Trimethidinium Methosulfate Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 400 mg. of trimethidinium methosulfate, to a 250-ml. conical flask, add 100.0 ml. of saturated sodium chloride solution, and shake mechanically for 1 hour. Filter, discarding the first 25 ml. of filtrate, and transfer 10.0 ml. of the clear filtrate to a 100-ml. beaker. Add 30 ml. of water and 5 ml. of a chloroplatinic acid solution (1 in 10) while stirring vigorously. Cool in an ice bath for about 3 hours, and then collect the precipitate on a tared, fine-porosity sintered-glass weighing funnel, completing the transfer with the aid of the cold filtrate. Wash the precipitate with two 5-ml. portions of cold water, followed by 50 ml. of ether. Dry the precipitate to constant weight at 105°, cool, and weigh. The weight of the chloroplatinate so obtained, multiplied by 0.7232, represents the equivalent of $C_{19}H_{42}N_2O_8S_2$ in the portion of the Tablets taken.

Packaging and storage—Preserve Trimethidinium Methosulfate Tablets in tight containers.

Tablets available—Trimethidinium Methosulfate Tablets usually available contain the following amount of trimethidinium methosulfate: 20 mg.

CATEGORY and DOSE—See Trimethidinium Methosulfate.

Trimethobenzamide Hydrochloride*



N-[*p*-[2-(Dimethylamino)ethoxy]benzyl]-3,4,5-trimethoxybenzamide Monohydrochloride

$C_{21}H_{28}N_2O_5 . HCl$ Mol. wt. 424.93

Trimethobenzamide Hydrochloride, dried at 105° for 4 hours, contains not less than 98.5 percent and not more than 100.5 percent of $C_{21}H_{28}N_2O_5 . HCl$.

Description—Trimethobenzamide Hydrochloride occurs as a white, crystalline powder. It has a slight phenolic odor.

Solubility—Trimethobenzamide Hydrochloride is soluble in water and in warm alcohol. It is insoluble in ether and in benzene.

Identification—

A: To 3 drops of a 1 in 10 solution of Trimethobenzamide Hydrochloride add 2 ml. of sulfuric acid: the light red color which is produced turns to deep red on heating on a steam bath for 3 minutes. Pour the cooled solution into 5 ml. of water: the color changes to light yellow and the solution exhibits a bluish green fluorescence under ultraviolet light.

B: Trimethobenzamide Hydrochloride responds to the tests for *Chloride*, page 808.

Melting range, page 814—Trimethobenzamide Hydrochloride melts between 187° and 190°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Trimethobenzamide Hydrochloride, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Trimethobenzamide Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 50,000 solution of Trimethobenzamide Hydrochloride in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Trimethobenzamide Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 258 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Trimethobenzamide Hydrochloride at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Trimethobenzamide Hydrochloride yields not more than 0.1 percent of residue on ignition.

Heavy metals, page 806—Dissolve 1 g. of Trimethobenzamide Hydrochloride in 20 ml. of water, add 2 ml. of diluted acetic acid, and dilute with water to 25 ml.: the heavy metals limit for Trimethobenzamide Hydrochloride is 20 parts per million.

Assay—Dissolve about 1.3 g. of Trimethobenzamide Hydrochloride, previously dried at 105° for 4 hours and accurately weighed, in 80 ml. of glacial acetic acid and 15 ml. of mercuric acetate T.S. Add 3 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 42.49 mg. of $C_{21}H_{28}N_2O_5 . HCl$.

Packaging and storage—Preserve Trimethobenzamide Hydrochloride in well-closed containers.

CATEGORY—Antiemetic.

USUAL DOSE RANGE—Oral and intramuscular, **100** to **250 mg**. four times a day; rectal, **200 mg.** three or four times a day.

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* Patented. See notice, page ii.

Trimethobenzamide Hydrochloride Capsules

Trimethobenzamide Hydrochloride Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{28}N_2O_5 . HCl$. Only lactose, magnesium stearate, starch, and talc may be present as added substances in the Capsules.

Identification—

A: Transfer a portion of the contents of Trimethobenzamide Hydrochloride Capsules, equivalent to 100 mg. of trimethobenzamide hydrochloride, to a separator containing 15 ml. of 0.1 *N* sodium hydroxide, and mix. Extract with a 10-ml. portion of chloroform, filtering the chloroform through anhydrous sodium sulfate into a 50-ml. beaker, and evaporate the filtrate to dryness on a steam bath with the aid of a stream of nitrogen. To the residue add 2 ml. of sulfuric acid: the light red color which is produced turns to deep red on heating on a steam bath for 3 minutes. Pour the cooled solution into 5 ml. of water: the color changes to light yellow and the solution exhibits a bluish green fluorescence under ultraviolet light.

B: The ultraviolet absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of the Reference Standard solution.

Weight variation, page 901—Trimethobenzamide Hydrochloride Capsules meet the requirements of the weight variation test for capsules.

Assay—Transfer as completely as possible the contents of not less than 20 Trimethobenzamide Hydrochloride Capsules to a suitable tared container, and determine the average weight per capsule. Mix the combined contents thoroughly and transfer an accurately weighed portion, equivalent to about 50 mg. of trimethobenzamide hydrochloride, to a 100-ml. volumetric flask. Add 50 ml. of 0.1 *N* hydrochloric acid, shake the mixture for several minutes, then dilute to volume with 0.1 *N* hydrochloric acid, and mix. Filter through a small retentive filter paper, discarding the first 20 ml. of filtrate. Transfer 4.0 ml. of the subsequent filtrate to a 100-ml. volumetric flask, dilute to volume with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trimethobenzamide Hydrochloride Reference Standard, in the same medium at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 258 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{21}H_{28}N_2O_5.HCl$ in the portion of the Capsules taken by the formula $2.5C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Trimethobenzamide Hydrochloride Capsules in well-closed containers.

Capsules available—Trimethobenzamide Hydrochloride Capsules usually available contain the following amounts of trimethobenzamide hydrochloride: 100 and 250 mg.

CATEGORY and DOSE—See Trimethobenzamide Hydrochloride.

Trimethobenzamide Hydrochloride Injection

Trimethobenzamide Hydrochloride Injection is a sterile solution of trimethobenzamide hydrochloride in water for injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{21}H_{28}N_2O_5 . HCl$.

Identification—

A: Transfer an accurately measured volume of Trimethobenzamide Hydrochloride Injection, equivalent to about 100 mg. of trimethobenzamide hydrochloride, to a separator containing 15 ml. of 0.1 *N* sodium hydroxide, and mix. Proceed as directed in *Identification test A* under *Trimethobenzamide Hydrochloride Capsules,* page 737, beginning with "Extract with a 10-ml. portion of chloroform . . . ." The Injection meets the requirements of the test.

B: The ultraviolet absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of the Reference Standard solution.

pH, page 824—The pH of Trimethobenzamide Hydrochloride Injection is between 4.8 and 5.2.

Pyrogen—Trimethobenzamide Hydrochloride Injection, diluted with pyrogen-free saline T.S. to a concentration of 2 g. of trimethobenzamide hydrochloride in 100 ml., meets the requirements of the *Pyrogen Test,* page 851, the test dose being 1 ml. per kg.

Other requirements—Trimethobenzamide Hydrochloride Injection meets the requirements under *Injections,* page 810.

Assay—Transfer to a suitable separator an accurately measured volume of Trimethobenzamide Hydrochloride Injection, equivalent to about 200 mg. of trimethobenzamide hydrochloride. Add 5 ml. of water and 3 ml. of 1 *N* hydrochloric acid, and extract with four 20-ml. portions of ether, discarding the ether extracts.

Transfer the aqueous layer to a 500-ml. volumetric flask, dilute to volume with water, and mix. Dilute 5.0 ml. of the solution to 100.0 ml. with 0.1 *N* hydrochloric acid, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trimethobenzamide Hydrochloride Reference Standard, in the same medium, at a concentration of about 20 mcg. per ml., in 1-cm. cells, at the maximum at about 258 mμ, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{21}H_{28}N_2O_5.HCl$ in each ml. of the Injection taken by the formula $10 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, V is the volume, in ml., of the Injection taken, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Trimethobenzamide Hydrochloride Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Trimethobenzamide Hydrochloride Injection usually available contains the following amounts of trimethobenzamide hydrochloride: 200 mg. in 2 ml. and 2 g. in 20 ml.

CATEGORY and DOSE—See Trimethobenzamide Hydrochloride.

Trimethobenzamide Hydrochloride and Benzocaine Suppositories

Trimethobenzamide Hydrochloride and Benzocaine Suppositories contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{28}N_2O_5.HCl$ (trimethobenzamide hydrochloride) and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{11}NO_2$ (benzocaine).

Identification—

Standard preparation, trimethobenzamide hydrochloride—Dissolve 200 mg. of NF Trimethobenzamide Hydrochloride Reference Standard in 10 ml. of water in a suitable separator, add 10 ml. of a saturated solution of sodium bicarbonate, mix, and extract with one 10-ml. portion of chloroform. Use the chloroform solution for spotting.

Standard preparation, benzocaine—Dissolve 30 mg. of NF Benzocaine Reference Standard in 10 ml. of chloroform.

Sample preparation—Disperse 1 Trimethobenzamide Hydrochloride and Benzocaine Suppository in 10 ml. of warm water in a suitable separator, add 10 ml. of a saturated solution of sodium bicarbonate, mix, and extract with one 10-ml. portion of chloroform. Use the chloroform solution for spotting.

Procedure—Perform thin-layer chromatography (see page 791), using both *Standard preparations* concurrently with the *Sample preparation*. Use a silica gel G plate, ethyl acetate-methanol solvent (9:1); spot 10 μl., and allow the solvent to ascend about 10 cm. Remove the plate, and allow it to air-dry. Cover the upper half of the plate and spray with potassium iodoplatinate T.S. Cover the lower half of the plate and spray with a solution prepared by dissolving 100 mg. of *p*-dimethylaminobenzaldehyde in 1 ml. of hydrochloric acid and diluting with alcohol to 100 ml. Trimethobenzamide hydrochloride produces a bluish purple spot at about R_f 0.05. Benzocaine produces a yellow spot at about R_f 0.6. The *Sample preparation* produces the same colored spots at R_f values similar to those produced by both *Standard preparations*.

Assay for trimethobenzamide hydrochloride—Transfer to a 200-ml. volumetric flask an accurately weighed portion of a mixed mass of 12 Trimethobenzamide Hydrochloride and Benzocaine Suppositories, equivalent to 1.2 g. of trimethobenzamide hydrochloride. Retain the remaining portion of the mass for the *Assay for benzocaine.* Add 100 ml. of glacial acetic acid to the flask, and heat on a steam bath to effect solution of the trimethobenzamide hydrochloride. Cool to room temperature, dilute to volume with glacial acetic acid, and mix. Filter the resulting suspension, discarding the first 25 ml. of filtrate. Pipet 100.0 ml. of filtrate into a 250-ml. conical flask, add 4 drops of crystal violet T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to the blue-green end-point. To the same solution add 15 ml. of mercuric acetate T.S., and again titrate with 0.1 *N* perchloric acid to the blue-green end-point. Perform a blank determination, and make any necessary correction. The volume of 0.1 *N* perchloric acid consumed by trimethobenzamide hydrochloride in the portion of the sample taken is the total volume of titrant used less the volume needed to obtain the first end-point. Each ml. of 0.1 *N* perchloric acid is equivalent to 42.49 mg. of $C_{21}H_{28}N_2O_5.HCl$.

Assay for benzocaine—

Standard preparation—Transfer about 30 mg. of NF Benzocaine Reference Standard, previously dried over phosphorus pentoxide for 3 hours and accurately weighed, to a 1000-ml. volumetric flask, add 20 ml. of alcohol to dissolve it, dilute to volume with water, and mix. Dilute 25.0 ml. of the solution to 200.0 ml. with water, and mix.

Assay preparation—Transfer to a 1000-ml. volumetric flask an accurately weighed portion of Trimethobenzamide Hydrochloride and Benzocaine Suppositories taken from the mixed mass of 12 suppositories, prepared for the *Assay for trimethobenzamide hydrochloride*, and equivalent to about 30 mg. of benzocaine. Add 20 ml. of alcohol, 300 ml. of water, and warm the mixture to disperse and dissolve the trimethobenzamide hydrochloride and the benzocaine. Dilute to volume with water, and mix. Pipet 25.0 ml. of the solution into a 200-ml. volumetric flask, dilute to volume with water, mix, and filter through a fine porosity sintered-glass funnel.

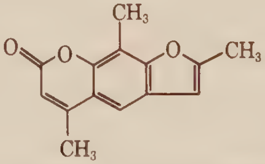
Procedure—Pipet into 3 individual 25-ml. volumetric flasks 10.0 ml. of the *Standard preparation*, 10.0 ml. of the *Assay preparation*, and 10.0 ml. of water to serve as the blank. To each flask add 5.0 ml. of water, 1.0 ml. of 4 N sulfuric acid, and 1.0 ml. of sodium nitrite solution (1 in 1000), mix, and allow to stand for 1 minute. Add 1.0 ml. of ammonium sulfamate solution (1 in 200), mix, allow to stand for 3 minutes, add 1.0 ml. of N-(1-naphthyl)ethylenediamine dihydrochloride solution (1 in 1000), dilute to volume with water, mix, and allow to stand for 15 minutes. Concomitantly determine the absorbances of the solutions, in 1-cm. cells at 540 mμ, with a suitable spectrophotometer, against the blank. Calculate the quantity, in mg., of $C_9H_{11}NO_2$ in the portion of the Suppositories taken by the formula $8C \times (A_U/A_S)$, in which A_U is the absorbance of the solution from the *Assay preparation*, A_S is the absorbance of the solution from the *Standard preparation*, and C is the exact concentration, in mcg. per ml., of the *Standard preparation*.

Packaging and storage—Preserve Trimethobenzamide Hydrochloride and Benzocaine Suppositories in well-closed containers in a cool place.

Suppositories available—Trimethobenzamide Hydrochloride and Benzocaine Suppositories usually available contain the following amount of trimethobenzamide hydrochloride: 200 mg., and 2 percent of benzocaine.

CATEGORY and DOSE—See Trimethobenzamide Hydrochloride.

Trioxsalen*



2,5,9-Trimethyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one

$C_{14}H_{12}O_3$ Mol. wt. 228.25

Trioxsalen contains not less than 97.0 percent and not more than 103.0 percent of $C_{14}H_{12}O_3$, calculated on the dried basis.

Caution: Avoid contact with the skin.

Description—Trioxsalen occurs as a white to off-white or grayish, odorless crystalline solid.

Solubility—Trioxsalen is sparingly soluble in chloroform, and is slightly soluble in alcohol. It is practically insoluble in water.

Melting range, page 814—Trioxsalen melts between 231° and 234°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Trioxsalen, previously dried at 105° for 6 hours, exhibits maxima only at the same wavelengths as that of NF Trioxsalen Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 200,000 solution of Trioxsalen in chloroform exhibits maxima and minima at the same wavelengths as that of NF Trioxsalen Reference Standard, similarly measured.

Loss on drying, page 814—Dry Trioxsalen at 105° for 6 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Trioxsalen yields not more than 0.5 percent of residue on ignition.

Assay—Transfer to a 100-ml. volumetric flask about 50 mg. of Trioxsalen, accurately weighed, add chloroform to volume, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Transfer to a third 100 ml. volumetric flask 10.0 ml. of this last solution, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trioxsalen Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 252 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{14}H_{12}O_3$ in the Trioxsalen taken by the formula $10C \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the Reference Standard solution, A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

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* Patented. See notice, page ii.

Packaging and storage—Preserve Trioxsalen in well-closed, light-resistant containers.

CATEGORY—Pigmenting agent (photosensitizer).

USUAL DOSE—**10 mg.** 2 hours before exposure to sunlight.

USUAL DOSE RANGE—**5 mg.** to **10 mg.**

Trioxsalen Tablets

Trioxsalen Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{14}H_{12}O_3$.

Identification—Triturate with 100 ml. of chloroform an amount of finely powdered Trioxsalen Tablets, equivalent to about 10 mg. of trioxsalen, and filter. On a suitable thin-layer chromatographic plate, coated with a 0.25-mm. layer of silica gel G, spot 5 μl. of this solution and 5 μl. of a chloroform solution of NF Trioxsalen Reference Standard containing 100 mcg. per ml. Allow the spots to dry, and develop the chromatogram, using methanol as the solvent, until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by viewing under an ultraviolet lamp: the R_f value of the main spot obtained from the sample solution corresponds to that obtained from the Reference Standard solution.

Disintegration, page 878—The disintegration time limit for Trioxsalen Tablets is 30 minutes.

Content uniformity, *Method I,* page 799—Trioxsalen Tablets meet the requirements of the content uniformity test for tablets.

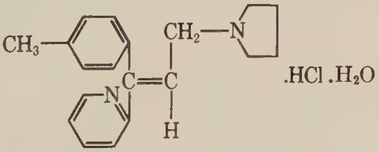
Assay—Weigh and finely powder not less than 20 Trioxsalen Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg. of trioxsalen, to a separator containing 25 ml. of water. Extract with three 25-ml. portions of chloroform, filtering each extract into a 100-ml. volumetric flask. Wash the filter with chloroform, dilute to volume with chloroform, and mix. Transfer 10.0 ml. of this solution to a second 100-ml. volumetric flask, dilute to volume with chloroform, and mix. Concomitantly determine the absorbance of this solution and of a solution of NF Trioxsalen Reference Standard, in the same medium, at a concentration of about 5 mcg. per ml., in 1-cm. cells, at the maximum at about 252 mμ, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg., of $C_{14}H_{12}O_3$ in the portion of the Tablets taken by the formula $C \times (A_U/A_S)$, in which C is the exact concentration of the Reference Standard solution, in mcg. per ml., A_U is the absorbance of the sample solution, and A_S is the absorbance of the Reference Standard solution.

Packaging and storage—Preserve Trioxsalen Tablets in well-closed, light resistant containers.

Tablets available—Trioxsalen Tablets usually available contain the following amount of trioxsalen: 5 mg.

CATEGORY and DOSE—See Trioxsalen.

Triprolidine Hydrochloride*



(*E*)-2-[3-(1-Pyrrolidinyl)-1-*p*-tolylpropenyl]pyridine Monohydrochloride

$C_{19}H_{22}N_2 . HCl . H_2O$ Mol. wt. 332.88

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* Patented. See notice, page ii.

Triprolidine Hydrochloride, dried in vacuum at 50° to constant weight, contains not less than 98.0 percent and not more than 101.0 percent of $C_{19}H_{22}N_2 . HCl$.

Description—Triprolidine Hydrochloride occurs as a white, crystalline powder having no more than a slight, but unpleasant, odor. Its solutions are alkaline to litmus, and it melts at about 115°.

Solubility—Triprolidine Hydrochloride is soluble in water, in alcohol, and in chloroform. It is insoluble in ether.

Identification—

A: A solution of Triprolidine Hydrochloride (1 in 20) yields a white to slightly yellow precipitate with mercuric-potassium iodide T.S.

B: A solution of Triprolidine Hydrochloride responds to the tests for *Chloride,* page 808.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Triprolidine Hydrochloride, previously dried in vacuum at 50° to constant weight, exhibits maxima only at the same wavelengths as that of NF Triprolidine Hydrochloride Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Triprolidine Hydrochloride in 0.1 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of NF Triprolidine Hydrochloride Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 290 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Triprolidine Hydrochloride in vacuum at 50° to constant weight: it loses not less than 3 percent and not more than 6 percent of its weight.

Residue on ignition, page 858—Triprolidine Hydrochloride yields not more than 0.1 percent of residue on ignition.

Arsenic—A *Test Preparation* prepared with 2.5 g. of Triprolidine Hydrochloride, as directed for organic compounds, meets the requirements of the *Arsenic Test,* page 777 (4 parts per million As).

Heavy Metals, *Method II,* page 806—The heavy metals limit for Triprolidine Hydrochloride is 20 parts per million.

Assay—Dissolve about 400 mg. of Triprolidine Hydrochloride, previously dried in vacuum at 50° to constant weight and accurately weighed, in 80 ml. of glacial acetic acid, warming if necessary to effect solution. Add 15 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 15.74 mg. of $C_{19}H_{22}N_2 . HCl$.

Packaging and storage—Preserve Triprolidine Hydrochloride in tight, light-resistant containers.

CATEGORY—Antihistaminic.

USUAL DOSE—**2.5 mg.** two or three times a day.

Triprolidine Hydrochloride Tablets

Triprolidine Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{19}H_{22}N_2 . HCl . H_2O$.

Identification—On a suitable thin-layer chromatographic plate (see page 791). coated with a 0.25-mm. layer of silica gel G, spot 1 μl. each of the *Standard preparation* and of the *Assay preparation* from the *Assay.* Allow the spots to dry, and then develop the chromatogram, in a chamber lined with blotting paper, with a solvent system consisting of chloroform and diethylamine (95:5) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Expose the plate to shortwave ultraviolet light for about 5 minutes, and then locate the spots by examining under longwave ultraviolet light. The R_f value of the main spot obtained from the *Assay preparation* corresponds to that obtained from the *Standard preparation.*

Disintegration, page 878—The disintegration time limit for Triprolidine Hydrochloride Tablets is 30 minutes.

Content uniformity, *Method II,* page 799—Triprolidine Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 250-ml. volumetric flask, add about 100 ml. of 0.1 *N* hydrochloric acid, and shake mechanically for 30 minutes. Dilute to volume with 0.1 *N* hydrochloric acid, mix, and filter, rejecting the first 100 ml. of filtrate. Dilute a portion of the subsequent filtrate quantitatively and stepwise, if necessary, with 0.1 *N* hydrochloric acid to provide a solution containing approximately 10 mcg. of triprolidine hydrochloride per ml. Concomitantly determine the absorbance of the final solution and of a solution of NF Triprolidine Hydrochloride Reference Standard, in the same medium, at a concentration of about 10 mcg. per ml., in 1-cm. cells, at the maximum at about 290 mμ, with a suitable spectrophotometer, using 0.1 N hydrochloric acid as the blank. Calculate the quantity, in mg., of $C_{19}H_{22}N_2.HCl.H_2O$ in the tablet by the formula $(T/D) \times C \times (A_U/A_S)$, in which T is the labeled quantity, in mg., of triprolidine hydrochloride in the tablet; D is the exact concentration, in mcg. per ml., of triprolidine hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; C is the exact concentration, in mcg. per ml., of $C_{19}H_{22}N_2.HCl.H_2O$ in the Reference Standard solution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—

Standard preparation—Transfer about 20 mg. of NF Triprolidine Hydrochloride Reference Standard, accurately weighed, to a glass-stoppered test tube, and proceed as directed under *Assay preparation*, beginning with "... add 20.0 ml. of water. ..."

Assay preparation—Weigh and finely powder not less than 20 Triprolidine Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg. of triprolidine hydrochloride, to a glass-stoppered test tube, add 20.0 ml. of water, and shake for 3 minutes. Add 2.0 ml. of 1 N sodium hydroxide solution, mix, then add 3.0 ml. of cyclohexane, and shake for 3 minutes. Centrifuge for 5 minutes, remove the clear supernatant liquid, and retain for use in the *Procedure*.

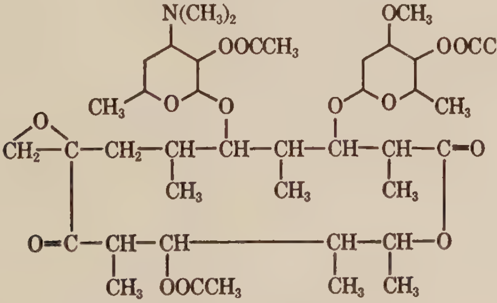
Procedure—Concomitantly determine the absorbances of the cyclohexane solutions in 1-mm. cells, with a suitable infrared spectrophotometer, at 12.13 μ, drawing a baseline from 11.9 μ to 12.4 μ, and using cyclohexane as the blank. Record the absorbance of the *Standard preparation* as A_S and that of the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{19}H_{22}N_2.HCl.H_2O$ in the portion of the Tablets taken by the formula $W \times (A_U/A_S)$, in which W is the exact weight, in mg., of $C_{19}H_{22}N_2.HCl.H_2O$ in the NF Triprolidine Hydrochloride Reference Standard taken for the *Standard preparation*.

Packaging and storage—Preserve Triprolidine Hydrochloride Tablets in tight, light-resistant containers.

Tablets available—Triprolidine Hydrochloride Tablets usually available contain the following amount of triprolidine hydrochloride: 2.5 mg.

CATEGORY and DOSE—See Triprolidine Hydrochloride.

Troleandomycin*



$C_{41}H_{67}NO_{15}$ Triacetyloleandomycin Mol. wt. 813.99

Troleandomycin is the triacetyl ester of oleandomycin. It has a potency of not less than 760 mcg. per mg. It conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Description—Troleandomycin occurs as a white, odorless, crystalline powder. A 1 in 100 solution of Troleandomycin in diluted alcohol has a pH between 7.5 and 9.0.

Solubility—Troleandomycin is soluble in alcohol. It is slightly soluble in ether and in water.

Packaging and storage—Preserve Troleandomycin in tight containers.

CATEGORY—Antibacterial.
USUAL DOSE—**250 mg.** four times a day.
USUAL DOSE RANGE—**250** to **500 mg.**

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* Patented. See notice, page ii.

Troleandomycin Capsules

Troleandomycin Capsules contain not less than 90.0 percent of the labeled amount of $C_{41}H_{67}NO_{15}$. Troleandomycin Capsules conform to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Troleandomycin Capsules in well-closed containers.

Capsules available—Troleandomycin Capsules usually available contain the following amounts of troleandomycin: 125 and 250 mg.

Category and Dose—See Troleandomycin.

Troleandomycin Oral Suspension

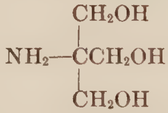
Troleandomycin Oral Suspension is a suspension of troleandomycin in an aqueous vehicle containing one or more suitable suspending and dispersing agents, colors, flavors, buffers, and preservatives. It contains not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{41}H_{67}NO_{15}$. Troleandomycin Oral Suspension conforms to the regulations of the federal Food and Drug Administration concerning certification of antibiotic drugs.

Packaging and storage—Preserve Troleandomycin Oral Suspension in tight containers.

Suspension available—Troleandomycin Oral Suspension usually available contains the following amount of troleandomycin: 125 mg. in 5 ml.

Category and Dose—See Troleandomycin.

Tromethamine



$$\begin{array}{rl} & \mathrm{CH_2OH} \\ & | \\ \mathrm{NH_2{-}} & \mathrm{CCH_2OH} \\ & | \\ & \mathrm{CH_2OH} \end{array}$$

2-Amino-2-(hydroxymethyl)-1,3-propanediol

$C_4H_{11}NO_3$ Mol. wt. 121.14

Tromethamine contains not less than 99.0 percent and not more than 101.0 percent of $C_4H_{11}NO_3$, calculated on the dried basis.

Description—Tromethamine occurs as a white, crystalline powder with a slight, characteristic odor.

Solubility—Tromethamine is freely soluble in water and in lower aliphatic alcohols. It is practically insoluble in chloroform, in benzene, and in carbon tetrachloride.

Identification—

A: To 4.5 ml. of a saturated solution of salicylaldehyde add 0.5 ml. of glacial acetic acid, and mix. Add 4.0 ml. of a 1 in 5 solution of Tromethamine, and mix: a yellow color is produced.

B: To 0.5 ml. of a 4 in 10 solution of ceric ammonium nitrate in 2 *N* nitric acid add 3 ml. of water and 0.5 ml. of a 1 in 5 solution of Tromethamine, and mix: the color changes from light yellow to orange.

Melting range, page 814—Tromethamine melts between 168° and 172°.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Tromethamine, previously dried at 105° for 3 hours, exhibits maxima only at the same wavelengths as that of NF Tromethamine Reference Standard, similarly measured.

pH, page 824—The pH of a solution of Tromethamine (1 in 20) is between 10.0 and 11.5.

Loss on drying, page 814—Dry Tromethamine at 105° for 3 hours: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Tromethamine yields not more than 0.05 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Tromethamine is 10 parts per million.

Assay—Dissolve about 180 mg. of Tromethamine, accurately weighed, in 100 ml. of water, add 3 drops of bromocresol purple T.S., and titrate with 0.1 *N* hydrochloric acid to a yellow end-point. Each ml. of 0.1 *N* hydrochloric acid is equivalent to 12.11 mg. of $C_4H_{11}NO_3$.

Packaging and storage—Preserve Tromethamine in tight containers.

CATEGORY—Alkalizer.

USUAL DOSE—Intravenous, **300 mg.** per kg. of body weight as a single dose with the average total dose being about **25 g.** given over a period of not less than 1 hour. Doses of up to **500 mg.** per kg. may be required depending upon the severity and progression of the acidosis.

Tromethamine for Injection

Tromethamine for Injection is a sterile, lyophilized mixture of tromethamine with potassium chloride and sodium chloride. It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_4H_{11}NO_3$ (tromethamine); and not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of KCl (potassium chloride) and of NaCl (sodium chloride).

Identification—

A: A solution of Tromethamine for Injection, prepared as recommended in the labeling, responds to the tests for *Chloride*, page 808, for *Sodium*, page 810, and for *Potassium*, page 809.

B: The infrared absorption spectrum of a mineral oil dispersion of Tromethamine for Injection exhibits maxima at the same wavelengths as that of NF Tromethamine Reference Standard, similarly measured, page 856.

pH, page 824—The pH of a solution of Tromethamine for Injection, prepared as recommended in the labeling, is between 10.0 and 11.5.

Water, page 900—Determine the water content of Tromethamine for Injection by the titrimetric method, adding 5 ml. of glacial acetic acid prior to the titration: not more than 1 percent of water is found.

Pyrogen—Tromethamine for Injection, diluted with water for injection to a concentration of 50 mg. of tromethamine per ml., meets the requirements of the *Pyrogen Test*, page 851, the test dose being 10 ml. per kg., injected slowly.

Other requirements—Tromethamine for Injection meets the requirements for *Sterility Tests*, page 874, *Weight Variation Test for Sterile Solids*, page 901, and *Labeling* under *Injections*, page 810.

Assay for tromethamine—Dissolve the entire contents of the container of Tromethamine for Injection in sufficient water, diluting to an accurately measured volume to obtain a solution containing about 36 mg. of tromethamine per ml. Transfer to a beaker an accurately measured volume of the solution, equivalent to about 180 mg of tromethamine, dilute to about 100 ml. with water, add 3 drops of bromocresol purple T.S , and titrate with 0.1 *N* hydrochloric acid to a yellow end-point. Each ml. of 0.1 *N* hydrochloric acid is equivalent to 12.11 mg. of $C_4H_{11}NO_3$.

Assay for potassium chloride—

Standard solutions—Prepare five standard solutions (*1*, *2*, *3*, *4*, and *5*) each containing 0.60 milliequivalents of sodium (35 mg. of sodium chloride) per liter, and to the solutions add, respectively, 0-, 2-, 4-, 6-, and 8-mg. supplements of potassium, in the form of the chloride, per liter. If necessary, because of changes in the sensitivity of the instrument mentioned below, vary the levels of concentration of the potassium, keeping the ratios between solutions approximately as given.

Standard graph—Set a suitable flame photometer for maximum transmittance at a wavelength of 766 mμ to 767 mμ. (The exact wavelength setting will vary slightly with the instrument.) Adjust the instrument to zero transmittance with solution *1*. Then adjust the instrument to 100 percent transmittance with solution *5*. Read the percentage transmittance of solutions *2*, *3*, and *4*. Plot the observed transmittance of solutions *2*, *3*, *4*, and *5* as the ordinate and the concentration, in mcg. per ml., of potassium as the abscissa on arithmetic coordinate paper.

Procedure—Dissolve the entire contents of the container of Tromethamine for Injection in sufficient water, and dilute quantitatively and stepwise to obtain a solution containing about 4 mcg. of potassium per ml., or a quantity corresponding to the concentration of the *Standard solutions*. Adjust the instrument to zero transmittance with solution *1*, and to 100 percent transmittance with solution *5*. Read the percentage transmittance of the test solution. By reference to the *Standard graph*, determine the concentration, in mcg. per ml., of potassium in the test solution, apply the dilution factor, and calculate the quantity, in mg., of potassium in the container of Tromethamine for Injection. Each mg. of potassium is equivalent to 1.907 mg. of potassium chloride (KCl).

Assay for sodium chloride—Proceed as directed under *Assay for potassium chloride*, with the following modifications: (1) Prepare the *Standard solutions* to contain 0, 2, 4, 6, and 8 mg. of sodium, in the form of the chloride, per 1000 ml., without added potassium; (2) prepare the *Standard graph* with the flame photometer set at 588 mμ to 589 mμ; and (3) under *Procedure* read "sodium" for "potassium" throughout. Each mg. of sodium is equivalent to 2.542 mg. of sodium chloride (NaCl).

Packaging and storage—Preserve Tromethamine for Injection in *Containers for Sterile Solids* as described under *Injections*, page 810.

Size available—Tromethamine for Injection usually available contains the following amounts of tromethamine, potassium chloride, and sodium chloride: 36 g. of tromethamine, 370 mg. of potassium chloride, and 1.75 g. of sodium chloride.

CATEGORY and DOSE—See Tromethamine.

Trypsin Crystallized

Trypsin Crystallized is a proteolytic enzyme crystallized from an extract of the pancreas gland of the ox, *Bos taurus* Linné (Fam. *Bovidæ*). When assayed as directed herein, it contains not less than 2500 NF Trypsin Units in each mg., calculated on the dried basis, and not less than 90.0 percent and not more than 110.0 percent of the labeled potency.

Note: Determine the suitability of the substrates and check the adjustment of the spectrophotometer by performing the assay using NF Trypsin Crystallized Reference Standard.

Description—Trypsin Crystallized occurs as a white to yellowish white, odorless, crystalline or amorphous powder.

Solubility test—An amount of Trypsin Crystallized, equivalent to 500,000 NF Trypsin Units, is soluble in 10 ml. of water or in 10 ml. of saline T.S.

Loss on drying, page 814—Dry Trypsin Crystallized in vacuum at 60° for 4 hours: it loses not more than 5 percent of its weight.

Residue on ignition, page 858—Trypsin Crystallized yields not more than 2.5 percent of residue on ignition.

Chymotrypsin—

Fifteenth molar phosphate buffer, pH 7.0—Dissolve 4.54 g. of monobasic potassium phosphate in sufficient water to make 500 ml. of solution. Dissolve 4.73 g. of anhydrous dibasic sodium phosphate in sufficient water to make 500 ml. of solution. Mix 38.9 ml. of the monobasic potassium phosphate solution with 61.1 ml. of dibasic sodium phosphate solution. If necessary, adjust the pH to 7.0 by the dropwise addition of dibasic sodium phosphate solution.

Substrate solution—Dissolve 23.7 mg. of *N*-acetyl-L-tyrosine ethyl ester, suitable for use in determining chymotrypsin, in about 50 ml. of *Fifteenth molar phosphate buffer, pH 7.0* with warming. When cool, dilute to 100 ml. with additional pH 7.0 buffer. (*Substrate solution* may be stored in the frozen state and used after thawing; it is important, however, to freeze immediately after preparation.)

Trypsin Crystallized solution—Dissolve a sufficient amount of Trypsin Crystallized, accurately weighed, in 0.001 *N* hydrochloric acid to produce a solution containing 650 NF Trypsin Units in each ml.

Procedure—Conduct the test in a suitable spectrophotometer equipped to maintain a temperature of 25° ± 0.1° in the cell compartment. The temperature in the reaction cell should be determined before and after the measurement of absorbance to assure that the temperature does not change by more than 0.5°. Pipet 0.2 ml. of 0.001 *N* hydrochloric acid and 3.0 ml. of the *Substrate solution* into a 1-cm. cell. Place this cell in the spectrophotometer and adjust the instrument so that the absorbance will read 0.200 at 237 mμ. Pipet 0.2 ml. of *Trypsin Crystallized solution* into another 1-cm. cell, add 3.0 ml. of the *Substrate solution*, and place the cell in the spectrophotometer. (*This order of addition must be followed.*) At the time the *Substrate solution* is added, start a stopwatch and read the absorbance at 30-second intervals for at least 5 minutes. Repeat the procedure on the same dilution at least once. Absolute absorbance values are of less importance than the constancy of the rate of change of absorbance. If the rate of change does not remain constant for at least 3 minutes, repeat the run and, if necessary, use a lower concentration. The duplicate run at the same dilution should match the first run in rate of absorbance change. Determine the average absorbance change per minute, using only the values within the 3-minute portion of the curve where the rate of absorbance is constant. Plot a curve of absorbance against time. One NF Chymotrypsin Unit is the activity causing a change in absorbance of 0.0075 per minute under the conditions specified in this test. Calculate the number of NF Chymotrypsin Units per mg. of Trypsin Crystallized by the formula $(A_2 - A_1)/(T \times W \times 0.0075)$, in which A_1 is the absorbance straight line final reading, A_2 is the absorbance straight line initial reading, T is the elapsed time in minutes between the initial and final readings, and W is the weight, in mg., of Trypsin Crystallized in the volume of solution used in determining the absorbance. No more than 50 NF Chymotrypsin Units per 2500 NF Trypsin Units are found, indicating the presence of not more than approximately 5 percent (w/w) of chymotrypsin.

Salmonella, page 862—The test for *Salmonella* in Trypsin Crystallized is negative.

Assay—

Fifteenth molar phosphate buffer, pH 7.6—Dissolve 4.54 g. of monobasic potassium phosphate in sufficient water to make 500 ml. of solution. Dissolve 4.73 g. of anhydrous dibasic sodium phosphate in sufficient water to make 500 ml. of solution. Mix 13 ml. of the monobasic potassium phosphate solution with 87 ml. of the anhydrous dibasic sodium phosphate solution.

Substrate solution—Dissolve 85.7 mg. of *N*-benzoyl-L-arginine ethyl ester hydrochloride, suitable for use in assaying Trypsin Crystallized (see *Note*), in sufficient water to make 100 ml. Dilute 10 ml. of this solution to 100 ml. with *Fifteenth molar phosphate buffer, pH 7.6*. Determine the absorbance of this solution at 253 mμ in a 1-cm. cell, using water as a blank, in a suitable spectrophotometer equipped with thermospacers to maintain a temperature of 25° ± 0.1°. By the addition of *Fifteenth molar phosphate buffer, pH 7.6*, or of the *Substrate solution* before dilution, adjust the absorbance so that it measures not less than 0.575 nor more than 0.585. Use this *Substrate solution* within a period of 2 hours.

Trypsin Crystallized solution—Dissolve a sufficient amount of Trypsin Crystallized, accurately weighed, in 0.001 *N* hydrochloric acid to produce a solution containing about 3000 NF Trypsin Units in each ml. Dilute this solution with 0.001 *N* hydrochloric acid to produce 3 solutions containing 12, 18, and 24 NF Trypsin Units, respectively, in each 0.2 ml. Use these three concentrations in the assay procedure.

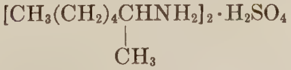
Procedure—Pipet 0.2 ml. of 0.001 *N* hydrochloric acid and 3.0 ml. of the *Substrate solution* into a 1-cm. cell. Place this cell in a spectrophotometer and adjust the instrument so that the absorbance will read 0.050 at 253 mμ. Pipet 0.2 ml. of *Trypsin Crystallized solution*, containing 12 NF Trypsin Units, into another 1-cm. cell, add 3.0 ml. of *Substrate solution*, and place the cell in the spectrophotometer. At the time the *Substrate solution* is added, start a stopwatch and read the absorbance at 30-second intervals for 5 minutes. Repeat the procedure with each of the solutions containing 18 and 24 NF Trypsin Units. Plot curves of absorbance against time for each concentration of the *Trypsin Crystallized solution* and use only those values which form a straight line to determine the activity of the Trypsin Crystallized. Discard values on the plateau and take the average of the results from the three concentration levels as the actual activity of the Trypsin Crystallized. One NF Trypsin Unit is the activity causing a change in absorbance of 0.003 per minute under the conditions specified in this assay. Calculate the number of NF Trypsin Units per mg. at each level by the formula $(A_1 - A_2)/(T \times W \times 0.003)$, in which A_1 is the absorbance straight line final reading, A_2 is the absorbance straight line initial reading, T is the elapsed time in minutes between the initial and final readings, and W is the weight, in mg., of Trypsin Crystallized in the volume of solution used in determining the absorbances.

Packaging and storage—Preserve Trypsin Crystallized in tight containers and avoid excessive heat.

CATEGORY—Proteolytic.

USUAL DOSE RANGE—Intramuscular, 12,500 to 25,000 NF Units daily. Buccal, 12,500 NF Units four times daily. Topical, as a wet dressing of a solution containing 10,000 NF Units per ml.

Tuaminoheptane Sulfate



$$[CH_3(CH_2)_4\underset{\substack{|\\ CH_3}}{C}HNH_2]_2\cdot H_2SO_4$$

1-Methylhexylamine Sulfate (2:1)

$(C_7H_{17}N)_2.H_2SO_4$ Mol. wt. 328.52

Tuaminoheptane Sulfate contains not less than 96.5 percent and not more than 100.5 percent of $(C_7H_{17}N)_2.H_2SO_4$, calculated on the dried basis.

Description—Tuaminoheptane Sulfate occurs as a white, odorless powder.

Solubility—Tuaminoheptane Sulfate is freely soluble in water, soluble in alcohol, and sparingly soluble in ether.

Identification—Dissolve 1.2 g. of Tuaminoheptane Sulfate in 25 ml. of water containing 1 g. of potassium cyanate. Heat the solution on a steam bath for 1 hour. Cool, filter the mixture, wash the crystals with water, and dry them at 105°: the derivative so obtained melts between 127° and 129°, page 814.

Loss on drying, page 814—Dry Tuaminoheptane Sulfate to constant weight at 105°: it loses not more than 1 percent of its weight.

Residue on ignition, page 858—Tuaminoheptane Sulfate yields not more than 0.1 percent of residue on ignition.

Assay—Accurately weigh about 1 g. of Tuaminoheptane Sulfate, dissolve in water in a 25-ml. volumetric flask, and dilute to volume with water. Transfer 5.0 ml. of the solution to an ammonia distillation apparatus, and add 200 ml. of water and 50 ml. of a solution of sodium hydroxide (1 in 2). Distil the amine into 20.0 ml. of 0.1 *N* hydrochloric acid until 150 ml. of distillate has been collected. Add 3 drops of methyl red T.S., and titrate the excess acid with 0.1 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* hydrochloric acid is equivalent to 16.43 mg. of $(C_7H_{17}N)_2.H_2SO_4$.

Packaging and storage—Preserve Tuaminoheptane Sulfate in tight containers.

CATEGORY—Adrenergic.

APPLICATION—To the nasal mucosa as a 0.5 to 2 percent solution.

Tuaminoheptane Sulfate Solution

Tuaminoheptane Sulfate Solution is a solution of tuaminoheptane sulfate in water adjusted to a suitable pH and tonicity. It contains a preservative. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $(C_7H_{17}N)_2.H_2SO_4$.

Tuaminoheptane Sulfate Solution may be prepared as follows:

Sodium Hydroxide	227	mg.
Phenylmercuric Nitrate	20	mg.
Potassium Phosphate, Monobasic	6.8	g.
Sodium Chloride	900	mg.
Tuaminoheptane Sulfate	10	g.
Purified Water, a sufficient quantity		
To make	1000	ml.

Dissolve the sodium hydroxide in 900 ml. of purified water, then dissolve the phenylmercuric nitrate, monobasic potassium phosphate, sodium chloride, and tuaminoheptane sulfate in this solution, and adjust the pH, if necessary, to between 5.8 and 6.2. Add sufficient purified water to make 1000 ml., mix thoroughly, and filter.

Identification—Transfer 50 ml. of Tuaminoheptane Sulfate Solution to a separator containing 2 ml. of sodium hydroxide solution (1 in 2), add 50 ml. of ether, and shake for 2 minutes. Allow the layers to separate, and discard the lower aqueous layer. Evaporate the ether layer to a volume of about 2 ml. Inject a portion of this solution into a suitable gas chromatograph (see page 787) equipped with a thermoconductivity detector, a 2-m. × 6-mm. (outside diameter) stainless steel column packed with 15 percent polyethylene glycol 4000 on sodium hydroxide-treated (5 percent sodium hydroxide) chromatographic siliceous earth. Adjust the column temperature to between 75° and 80°; other instrumental parameters must be adjusted according to the particular instrument being used. The sample chromatogram conforms qualitatively to that of a chromatogram obtained from NF Tuaminoheptane Sulfate Reference Standard, similarly measured.

pH, page 824—The pH of Tuaminoheptane Sulfate Solution is between 5.8 and 6.2.

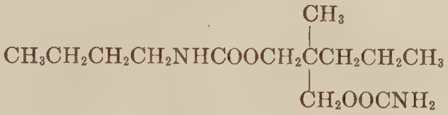
Assay—Transfer an accurately measured volume of Tuaminoheptane Sulfate Solution, equivalent to about 200 mg. of tuaminoheptane sulfate, to a 500-ml. ammonia distillation apparatus, and add 200 ml. of water and a few glass beads. Connect the apparatus to a receiver containing 40.0 ml. of 0.05 *N* hydrochloric acid. Add 50 ml. of sodium hydroxide solution (1 in 2) to the sample solution, and distil until 200 ml. of distillate has been collected. Cool the distillate, add 3 drops of methyl red T.S., and titrate the excess acid with 0.02 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.05 *N* hydrochloric acid is equivalent to 8.213 mg. of $(C_7H_{17}N)_2 . H_2SO_4$.

Packaging and storage—Preserve Tuaminoheptane Sulfate Solution in tight containers.

Solution available—Tuaminoheptane Sulfate Solution usually available contains 1 percent of tuaminoheptane sulfate.

Category and Dose—See Tuaminoheptane Sulfate.

Tybamate*



$$CH_3CH_2CH_2CH_2NHCOOCH_2\underset{CH_2OOCNH_2}{\overset{CH_3}{C}}CH_2CH_2CH_3$$

2-(Hydroxymethyl)-2-methylpentyl Butylcarbamate Carbamate

$C_{13}H_{26}N_2O_4$ Mol. wt. 274.36

Tybamate contains not less than 98.0 percent and not more than 102.0 percent of $C_{13}H_{26}N_2O_4$, calculated on the dried basis.

Description—Tybamate occurs as a white, crystalline powder or as a clear, viscous liquid which may congeal to a solid form on standing. It has a mild characteristic odor and a bitter taste.

Solubility—Tybamate is very slightly soluble in water, very soluble in alcohol and in acetone, and freely soluble in ether.

Identification—

A: Mix 1 ml. of a 1 in 2500 solution of Tybamate in chloroform with 1 ml. of a 1 in 4 mixture of glacial acetic acid and acetone, add 1 ml. of a 1 in 100 solution of *p*-dimethylaminobenzaldehyde in benzene, 4 ml. of antimony trichloride T.S., and 1 ml. of acetic anhydride, and heat at about 55° for 15 minutes: a red color is produced.

B: Dissolve 1 g. of Tybamate and 800 mg. of xanthydrol in a mixture of 10 ml. of dehydrated alcohol and 10 ml. of glacial acetic acid, and heat on a steam bath for 90 minutes, avoiding excessive evaporation. Cool, and add cold water: an oil, which may crystallize on standing, separates from the solution. Filter the mixture through paper, wash the residue with water until free from acetic acid odor, and dry at 105° for 2 hours: the residue, when recrystallized from a 1 in 3 mixture of trichloroethylene and hexane, melts between 127° and 130°, page 814.

Melting range, page 814—Crystalline Tybamate, previously dried in vacuum at 30° to 35° for 4 hours, melts within a range of 2° between 49° and 54°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Tybamate, previously dried in vacuum at 30° to 35° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Tybamate Reference Standard, similarly measured.

Loss on drying, page 814—Dry Tybamate in vacuum at 30° to 35° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Tybamate yields not more than 0.1 percent residue on ignition. Retain the residue from 1 g. for the *Heavy metals test*.

Heavy metals, page 806—Dissolve the residue obtained in the test for *Residue on ignition* in a small volume of hot nitric acid, and evaporate to dryness on a steam bath. Dissolve the residue in 2 ml. of diluted acetic acid, and dilute to 25 ml. with water: the heavy metals limit for Tybamate is 10 parts per million.

Assay—Dissolve about 750 mg. of Tybamate, accurately weighed, in 20 ml. of pyridine, add 3 drops of phenolphthalein T.S., and then add 0.1 *N* sodium methoxide to the appearance of the first pink color. Add 50.0 ml. of 0.1 *N* sodium methoxide and a few boiling chips, and reflux with an air condenser on a steam bath for 30 minutes. Cool, add 40 ml. of neutralized alcohol, and titrate the excess sodium methoxide with 0.1 *N* hydrochloric acid to the absence of a pink color. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* sodium methoxide is equivalent to 27.44 mg. of $C_{13}H_{26}N_2O_4$.

Packaging and storage—Preserve Tybamate in tight containers.

Category—Tranquilizer (minor).

Usual dose range—**750 mg.** to **2 g.** daily in divided doses.

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* Patented. See notice, page ii.

Tybamate Capsules

Tybamate Capsules contain not less than 92.0 percent and not more than 108.0 percent of the labeled amount of $C_{13}H_{26}N_2O_4$.

Identification—

A: Transfer a portion of the contents of Tybamate Capsules, equivalent to about 30 mg. of tybamate, to a separator containing 25 ml. of chloroform, extract three times with 25-ml. portions of water, and discard the water extracts. Filter the chloroform solution, retain 1 ml. of the filtrate for *Identification test B*, and evaporate to dryness. The infrared absorption spectrum of a potassium bromide dispersion of the residue of tybamate, so obtained, exhibits maxima at the same wavelengths as that of NF Tybamate Reference Standard, similarly measured.

B: Mix 1 ml. of the filtrate obtained in *Identification test A* with 2 ml. of chloroform: 1 ml. of this solution meets the requirements of *Identification test A* under *Tybamate*, page 749.

Weight variation, page 901—Tybamate Capsules meet the requirements of the weight variation test for soft gelatin capsules.

Assay—Transfer as completely as possible the contents of not less than 20 Tybamate Capsules to a tared weighing bottle, and weigh. Dissolve an accurately weighed portion of the liquid, equivalent to about 750 mg. of tybamate, in 20 ml. of pyridine, and proceed as directed in the *Assay* under *Tybamate*, page 749, beginning with ". . . add 3 drops of phenolphthalein T.S. . . ."

Packaging and storage—Preserve Tybamate Capsules in tight, light-resistant containers.

Capsules available—Tybamate Capsules usually available contain the following amounts of tybamate: 125, 250, and 350 mg.

CATEGORY and DOSE—See Tybamate.

Tyrothricin

Tyrothricin is an antibacterial substance produced by the growth of *Bacillus brevis* Dubos (Fam. *Bacteriaceæ*). It consists principally of gramicidin and tyrocidine, the tyrocidine usually being present as the hydrochloride. Tyrothricin has a potency of not less than 900 mcg. and not more than 1400 mcg. in each mg. Tyrothricin conforms to the regulations of the federal Food and Drug Administraton concerning certification of antibiotic drugs.

Description—Tyrothricin occurs as a white, grayish white, or brownish white powder. It is odorless, or nearly odorless, and is almost tasteless.

Solubility—Tyrothricin is soluble in alcohol, usually leaving a small amount of residue. Tyrothricin is practically insoluble in water. It is freely soluble in glacial acetic acid, is slightly soluble in acetone, but is insoluble in chloroform and in ether.

Packaging and storage—Preserve Tyrothricin in tight containers.

CATEGORY—Antibacterial.

APPLICATION—Topically, to the skin and mucous membrane in dosage forms which contain from 0.05 to 0.3 percent of Tyrothricin.

Undecylenate, Zinc, page 767

Undecylenic Acid

$CH_2{=}CHCH_2(CH_2)_6CH_2COOH$

10-Undecenoic Acid

$C_{11}H_{20}O_2$ Mol. wt. 184.28

Undecylenic acid contains not less than 95.0 percent and not more than 100.5 percent of $C_{11}H_{20}O_2$.

Description—Undecylenic Acid is a clear, colorless to pale yellow liquid having a characteristic odor.

Solubility—Undecylenic Acid is almost insoluble in water. It is miscible with alcohol, with chloroform, with ether, with benzene, and with fixed and volatile oils.

Identification—

A: To 1 ml. of Undecylenic Acid add potassium permanganate T.S., dropwise: the permanganate color is discharged.

B: Place 3 ml. of Undecylenic Acid and 3 ml. of freshly distilled aniline in a tall test tube, and heat for 10 minutes at a rate such that the ring of condensate remains just below the mouth of the tube. Cool, add 10 ml. of alcohol and 10 ml. of ether, and transfer to a separator. Wash the ether solution with four 20-ml. portions of water, and discard the water washings. Heat on a steam bath until the odor of ether is no longer perceptible, then add a few mg. of activated carbon, mix well, and filter. Evaporate the filtrate nearly to dryness, and recrystallize the residue from 70 percent alcohol: the anilide so obtained melts between 66° and 67.5°, page 814.

Specific gravity, page 866—The specific gravity of Undecylenic Acid is not less than 0.910 and not more than 0.913.

Congealing range, page 794—Undecylenic Acid does not congeal below 21°.

Refractive index, page 858—The refractive index of Undecylenic Acid is not less than 1.447 and not more than 1.448.

Water-soluble acids—Shake 5 ml. of Undecylenic Acid with 5 ml. of water, and filter the water layer through a filter paper previously moistened with water. Add 1 drop of methyl orange T.S., and titrate with 0.1 *N* sodium hydroxide: not more than 0.1 ml. of 0.1 *N* sodium hydroxide is required to match the color produced by 1 drop of methyl orange T.S. in 5 ml. of water.

Residue on ignition, page 858—Undecylenic Acid yields not more than 0.15 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Undecylenic Acid is 10 parts per million.

Neutral fat—Boil 1 ml. of Undecylenic Acid with about 500 mg. of sodium carbonate and 30 ml. of water in a large flask: the resulting solution, while hot, is clear or, at most, opalescent.

Iodine value, page 804—The iodine value of Undecylenic Acid is not less than 131 and not more than 138.

Assay—Dissolve about 750 mg. of Undecylenic Acid, accurately weighed, in 50 ml. of alcohol, add 3 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to the first pink color which persists for at least 30 seconds. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 18.43 mg. of $C_{11}H_{20}O_2$.

Packaging and storage—Preserve Undecylenic Acid in well-closed, light-resistant containers.

CATEGORY—Local antifungal.

FOR EXTERNAL USE—Topically as a 1 to 10 percent ointment as required.

Compound Undecylenic Acid Ointment*

Compound Undecylenic Acid Ointment contains not less than 18.0 percent and not more than 22.0 percent of $C_{22}H_{38}O_4Zn$ (zinc undecylenate) and not less than 4.5 percent and not more than 5.5 percent of $C_{11}H_{20}O_2$ (free undecylenic acid).

Undecylenic Acid	**50 g.**
Zinc Undecylenate	**200 g.**
Polyethylene Glycol Ointment	**750 g.**
To make	**1000 g.**

Melt the polyethylene glycol ointment on a water bath at a temperature of about 65° and add the undecylenic acid and the zinc undecylenate. Remove from the water bath and stir until congealed and all ingredients are well mixed.

NOTE: In order to provide a product of suitable consistency under various climatic conditions, the proportions of the polyethylene glycol constituents of polyethylene glycol ointment may be altered, or another suitable ointment base may be used. However, the proportion of active ingredients must not be varied.

Assay for zinc undecylenate—Transfer to a 500-ml. Kjeldahl flask about 3 g. of Compound Undecylenic Acid Ointment, accurately weighed, add 50 ml. of nitric acid and 25 ml. of sulfuric acid, then add, cautiously, enough water to make about 250 ml. Add a few glass beads, heat the liquid to boiling, and continue the heating until fumes of sulfur trioxide are evolved. Add, dropwise, 1 ml. of nitric acid, and again heat until fumes of sulfur trioxide are evolved, and repeat the addition of 1 ml. of nitric acid and heating until the solution remains pale yellow in color. Cool, add, cautiously, 40 ml. of water, and boil until the solution becomes colorless. Cool the solution, add 50 ml. of water, mix, and filter into a 250-ml. volumetric flask, washing the reaction flask and the filter with several portions of water and collecting the washings in the volumetric flask. Dilute to volume with water, mix, and pipet 100.0 ml. of the solution into a 250-ml. beaker. Add ammonia T.S. until the solution is neutral to litmus paper, add 5 ml. of acetic acid solution (1 in 10) and 2 g. of sodium acetate, mix, heat the solution to 60°, and add slowly, with constant stirring, 5 ml. of 8-hydroxyquinoline T.S. If the supernatant is not yellow in color, add more 8-hydroxyquinoline T.S. Heat the mixture to boiling, allow to stand for 1 hour, filter through a tared filter crucible, and wash the precipitate with water until the total volume of filtrate is about 300 ml. Dry the crucible and contents at 130° for 2 hours, cool, and weigh. Calculate the quantity of $C_{22}H_{38}O_4Zn$ in the portion of the Ointment taken by the formula $2.5 \times 1.221 \times W$, in which 2.5 corrects for the aliquot used, 1.221 is the factor converting zinc hydroxyquinolinate ($C_{18}H_{12}N_2O_2Zn$) to zinc undecylenate, and W is the weight of zinc hydroxyquinolinate obtained.

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* Patented. See notice, page ii.

Assay for undecylenic acid—Transfer to a 250-ml. beaker about 5 g. of Compound Undecylenic Acid Ointment, accurately weighed, form a slurry by mixing with 100 ml. of dilute hydrochloric acid (1 in 10), heat the mixture to 70°, with constant stirring, allow it to cool to about 25°, and transfer it to a 500-ml. separator. Rinse the beaker with 100 ml. of ether, adding the rinsings to the mixture in the separator, dilute the aqueous phase to about 300 ml. with water, saturate the aqueous phase with sodium chloride to aid the extraction, and shake the mixture. Allow the layers to separate, transfer the ether layer to a second separator, and extract the aqueous layer with another 100-ml. portion of ether. Wash the combined ether extracts with 10-ml. portions of water until a portion of the washing is free from hydrochloric acid, transfer the ether solution to a 400-ml. beaker, and evaporate to about 5 ml. on a steam bath. Add 20 ml. of carbon tetrachloride, mix, transfer the mixture to a small separator, and carefully drain the carbon tetrachloride layer into a 100-ml. volumetric flask. Rinse the beaker with three 5-ml. portions of carbon tetrachloride, transferring the rinsings, separated from any occluded water, to the volumetric flask, and make to volume with carbon tetrachloride. Transfer 50.0 ml. of the solution to a 500-ml. conical flask, carefully evaporate to about 5 ml. on a hot plate, add 100 ml. of neutralized alcohol and 3 drops of phenolphthalein T.S., and titrate the total free and liberated undecylenic acid with 0.1 N sodium hydroxide. Each ml. of 0.1 N sodium hydroxide is equivalent to 18.43 mg. of $C_{11}H_{20}O_2$. The difference between the total undecylenic acid and the undecylenic acid equivalent to the determined zinc undecylenate (the weight of zinc undecylenate multiplied by 0.8533 gives the equivalent of undecylenic acid), both expressed as percent of the Ointment, gives the percent of $C_{11}H_{20}O_2$ (free undecylenic acid) in the Ointment.

Packaging and storage—Preserve Compound Undecylenic Acid Ointment in tight containers and avoid prolonged exposure to temperatures above 30°.

Category—Local antifungal.

Urethan

$NH_2COOC_2H_5$

Ethyl Carbamate

$C_3H_7NO_2$ Mol. wt. 89.09

Urethan contains not less than 99.0 percent and not more than 101.0 percent of $C_3H_7NO_2$, calculated on the anhydrous basis.

Description—Urethan occurs as colorless crystals or as a white, granular powder. It is odorless, or nearly so. Its solutions are neutral to litmus.

Solubility—Urethan is very soluble in water. It is freely soluble in alcohol, in glycerin, in chloroform, and in ether, and is sparingly soluble in olive oil.

Identification—

A: To 5 ml. of sulfuric acid add 1 g. of Urethan, and heat gently: decomposition occurs with the evolution of carbon dioxide.

B: Heat 1 g. of Urethan with 5 ml. of sodium hydroxide T.S.: ammonia, recognizable by its odor, is evolved.

C: Dissolve about 500 mg. of Urethan in 5 ml. of water, add about 1 g. of sodium carbonate and about 10 mg. of iodine, and warm the solution: yellow crystals of iodoform separate on cooling.

Melting range, page 814—Urethan melts between 48° and 50°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Urethan, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of NF Urethan Reference Standard, similarly measured.

Water, page 900—Determine the water content of Urethan by the titrimetric method: not more than 1 percent is found.

Residue on ignition, page 858—Urethan yields not more than 0.1 percent of residue on ignition.

Completeness and color of solution—A solution of 1 g. of Urethan in 5 ml. of alcohol is practically complete and is colorless.

Chloride, page 784—A 500-mg. portion of Urethan shows no more chloride than corresponds to 0.1 ml. of 0.02 *N* hydrochloric acid (0.014 percent).

Nitrate—Mix 2 ml. of a solution of Urethan (1 in 20) with 1 ml. of ferrous sulfate T.S. in a small test tube, and carefully add 2 ml. of sulfuric acid so as to form separate layers: no red or brown zone appears.

Heavy metals, page 806—Dissolve 1 g. of Urethan in water to make 24 ml., and add 1 ml. of 0.1 *N* hydrochloric acid: the heavy metals limit for Urethan is 10 parts per million.

Urea—Dissolve about 2 g. of Urethan in 2 ml. of water, and add 5 ml. of nitric acid: no white precipitate is formed.

Assay—Transfer about 250 mg. of Urethan, accurately weighed, into a conical flask, add 20 ml. of pyridine, and neutralize the solution with 0.1 *N* sodium methoxide to the first pink color of phenolphthalein T.S. Add 50.0 ml. of 0.1 *N* sodium methoxide and a few boiling chips, and reflux with an air condenser on a steam bath for 30 minutes. Cool, add 40 ml. of neutralized alcohol, and titrate the excess base with 0.1 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* sodium methoxide is equivalent to 8.909 mg. of $C_3H_7NO_2$.

Packaging and storage—Preserve Urethan in well-closed containers, preferably at a temperature not exceeding 30°.

CATEGORY—Antineoplastic.
USUAL DOSE—**3 g.** daily.
USUAL DOSE RANGE—**2** to **6 g.**

Urethan Tablets

Urethan Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_3H_7NO_2$.

Identification—

A: Powder a number of Urethan Tablets, equivalent to about 2 g. of urethan, triturate the powder with 10 ml. of water, and filter: the filtrate responds to *Identification tests B* and *C* under *Urethan*, page 752.

B: Transfer a quantity of powdered Urethan Tablets, equivalent to about 100 mg. of urethan, to a glass-stoppered conical flask. Add 10 ml. of chloroform, shake vigorously for about 5 minutes, filter, and evaporate to dryness. The infrared absorption spectrum of a potassium bromide dispersion prepared from the residue exhibits maxima only at the same wavelengths as that of NF Urethan Reference Standard, similarly measured.

Disintegration, page 787—The disintegration time limit for Urethan Tablets is 30 minutes.

Weight variation, page 901—Urethan Tablets meet the requirements of the weight variation test for tablets.

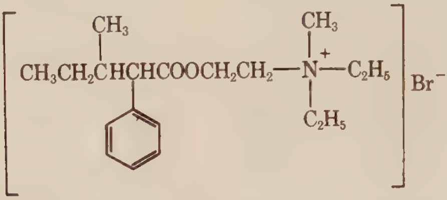
Assay—Weigh and finely powder not less than 20 Urethan Tablets. Transfer a portion of the powder, accurately weighed and equivalent to about 3 g. of urethan, to a 200-ml. volumetric flask, add water to volume, and mix. Filter, and transfer a 10.0-ml. portion of the filtrate to a Kjeldahl flask, then dilute with water to about 30 ml. Add 20 ml. of hydrochloric acid, and reflux gently for 3 hours. Cool thoroughly, dilute with about 150 ml. of water, again cool the mixture, and determine the nitrogen content as directed for *Method I*, page 821, using 0.1 *N* sulfuric acid for the titration. Each ml. of 0.1 *N* sulfuric acid is equivalent to 8.909 mg. of $C_3H_7NO_2$.

Packaging and storage—Preserve Urethan Tablets in well-closed containers.

Tablets available—Urethan Tablets usually available contain the following amount of urethan: 300 mg.

CATEGORY and DOSE—See Urethan.

Valethamate Bromide*



Diethyl(2-hydroxyethyl)methylammonium Bromide 3-Methyl-2-phenylvalerate

$C_{19}H_{32}BrNO_2$ Mol. wt. 386.38

Valethamate Bromide contains not less than 97.0 percent and not more than 100.5 percent of $C_{19}H_{32}BrNO_2$, calculated on the dried basis.

Description—Valethamate Bromide occurs as a white, crystalline powder. It is nearly odorless and is stable in air.

Solubility—Valethamate Bromide is freely soluble in water. It is very soluble in alcohol and is practically insoluble in ether.

Identification—To 5 ml. of a solution of Valethamate Bromide (1 in 100) add 4 ml. of diluted sulfuric acid, and then add 5 drops of sodium hypochlorite T.S. diluted with an equal volume of water. Add 5 ml. of carbon tetrachloride, shake vigorously, and allow the layers to separate: the carbon tetrachloride layer is brownish-red. (*Caution:* An excess of sodium hypochlorite T.S. will prevent the color formation.)

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Valethamate Bromide, previously dried in vacuum over phosphorus pentoxide for 4 hours, exhibits maxima only at the same wavelengths as that of NF Valethamate Bromide Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 1000 solution of Valethamate Bromide in methanol exhibits maxima and minima at the same wavelengths as that of NF Valethamate Bromide Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorption occurring at about 259 mμ, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Valethamate Bromide in vacuum over phosphorus pentoxide for 4 hours: it loses not more than 0.1 percent of its weight.

Assay—Dissolve about 700 mg. of Valethamate Bromide, accurately weighed, in 50 ml. of glacial acetic acid, add 10 ml. of mercuric acetate T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid, determining the end-point potentiometrically. Each ml. of 0.1 *N* perchloric acid is equivalent to 38.64 mg. of $C_{19}H_{32}BrNO_2$.

Packaging and storage—Preserve Valethamate Bromide in tight containers.

CATEGORY—Anticholinergic.

USUAL DOSE RANGE—Intramuscular and intravenous, **10** to **20 mg.** every 4 to 6 hours up to a maximum dosage of **60 mg.** in a 24-hour period.

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* Patented. See notice, page ii.

Valethamate Bromide Injection

Valethamate Bromide Injection is a sterile solution of valethamate bromide in water for injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{19}H_{32}BrNO_2$.

Identification—A portion of Valethamate Bromide Injection, equivalent to about 50 mg. of valethamate bromide, responds to the *Identification test* under *Valethamate Bromide*, page 754.

Pyrogen—Valethamate Bromide Injection meets the requirements of the *Pyrogen Test*, page 851, the test dose being 1.5 mg. per kg.

pH, page 824—The pH of Valethamate Bromide Injection is between 4.8 and 5.2.

Other requirements—Valethamate Bromide Injection meets the requirements under *Injections*, page 810.

Assay—

Standard preparation—Weigh accurately about 100 mg. of NF Valethamate Bromide Reference Standard, previously dried for 4 hours in vacuum over phosphorus pentoxide, and dissolve in sufficient water to make 100.0 ml. Transfer 30.0 ml. of this solution to a 250-ml. centrifuge bottle, and add 30 ml. of chloroform, 5 ml. of diluted sulfuric acid, and 1 ml. of a 1 in 10,000 solution of *p*-dimethylaminoazobenzene in alcohol.

Assay preparation—Transfer an accurately measured volume of Valethamate Bromide Injection, equivalent to about 30 mg. of valethamate bromide, to a 250-ml. centrifuge bottle, dilute to 30 ml. with water, and add 30 ml. of chloroform, 5 ml. of diluted sulfuric acid, and 1 ml. of a 1 in 10,000 solution of *p*-dimethylaminoazobenzene in alcohol.

Procedure—Titrate the *Standard preparation* and the *Assay preparation* with a solution of sodium lauryl sulfate (1 in 1000), shaking vigorously with each addition, to an end-point of the first permanent pink color in the chloroform layer. Record the volume, in ml., of titrant required for the *Standard preparation* as T_S and that required for the *Assay preparation* as T_U. Calculate the quantity, in mg., of $C_{19}H_{32}BrNO_2$ in each ml. of the Injection taken by the formula $(W/V) \times (T_U/T_S)$, in which W is the exact quantity, in mg., of NF Valethamate Bromide Reference Standard in the volume of the *Standard preparation* taken, and V is the volume in ml. of Injection taken.

Packaging and storage—Preserve Valethamate Bromide Injection in single-dose or multiple-dose containers, preferably of Type I glass.

Injection available—Valethamate Bromide Injection usually available contains the following amount of valethamate bromide: 50 mg. in 5 ml.

CATEGORY and DOSE—See Valethamate Bromide.

Vanilla

Vanilla is the cured, full-grown, unripe fruit of *Vanilla planifolia* Andrews, often known in commerce as Mexican or Bourbon Vanilla, or of *Vanilla tahitensis* J. W. Moore, known in commerce as Tahiti Vanilla (Fam. *Orchidaceæ*).

Vanilla yields not less than 12.0 percent of anhydrous extractive soluble in diluted alcohol.

Unground Vanilla—Unground Vanilla occurs as a linear, flattened capsule, from 12 to 35 cm. in length and from 5 to 9 mm. in width; having an apex terminating in a flat, circular scar, and a base gradually tapering, more or less curved or hooked, or in Tahiti Vanilla, broad in the middle and tapering toward either end, the base closely resembling the summit. It is flexible and tough; externally nearly black, dusky brown to moderate brown, longitudinally wrinkled, moist, glossy, and occasionally with an efflorescence of acicular or prismatic crystals of vanillin. Internally it is unilocular, with a brownish black pulp and numerous minute seeds. Occasional capsules are split near the summit into 3 parts. The odor and taste are characteristic, agreeably fragrant, and aromatic.

Histology—Vanilla shows an epidermis with a distinct cuticle and occasional stomata, the epidermal cells containing red to brown bodies, occasional prisms of calcium oxalate or crystals of vanillin; a collenchyma layer of 1 or 2 rows of cells; a thick sarcocarp, composed of parenchyma and an interrupted circle of fibrovascular bundles, the latter lepto-centric with a few vessels, and an outer circle of fibers with thin, strongly lignified walls and numerous transverse simple pits; the vessels with walls having slit-like pits or spiral thickenings; the parenchyma cells usually thin-walled and deeply undulate, some thick-walled with oblique, slit-like pits or broad spiral bands, and containing occasional bundles of acicular crystals of calcium oxalate up to 400 μ in length, or a thin protoplasmic layer enclosing numerous oil globules; an endocarp composed of placental and interplacental regions; the placental region consisting of 6 bifid placentas extending into the cavity of the fruit and bearing irregularly trianguloid, black to reddish, flattened seeds having a deeply reticulate seed-coat and up to about 250 μ in diameter; the interplacental regions showing long, nearly straight hairs more or less matted together by their gummy resinous secretion.

Powdered Vanilla—Powdered Vanilla is dusky brown to nearly black. The principal elements of identification are fragments of parenchyma of the sarcocarp with long, oblique, slit-like walls or broad spiral bands, calcium oxalate crystals of acicular outline and up to 400 μ in length, and monoclinic prisms up to 35 μ in length, numerous unicellular, nearly straight glandular hairs, fragments of the seed-coat with polygonal stone cells, and the slender crystals of vanillin.

Test for vanillin—Place a few of the crystals, occurring as an efflorescence on the fruit, on a micro-slide or watch glass, and add a drop of phloroglucinol T.S. and a drop of hydrochloric acid: the solution immediately acquires a red color.

Assay—Place 2 g. of Vanilla, finely cut or in coarse powder and accurately weighed, in a suitable flask. Add 70 ml. of diluted alcohol, shake the mixture for 2 hours in a mechanical shaker or during 8 hours at about 30-minute intervals, and allow to stand overnight. Decant the liquid onto a filter, and wash the flask and residue with small portions of diluted alcohol, passing the washings through the filter until the filtrate measures 100.0 ml. Mix the filtrate well, evaporate a 50.0-ml. portion to dryness in a suitable tared container on a steam bath, and dry the residue at 105° for 4 hours. The weight obtained represents the yield of anhydrous extractive soluble in diluted alcohol from 1 g. of Vanilla.

Packaging and storage—Preserve Vanilla in tight containers in a cold place.

Labeling—The commercial variety of Vanilla, whether Mexican, Bourbon, or Tahiti Vanilla, is stated on the label.

Note: Do not use Vanilla which has become brittle.

Category—Flavor.

Vanilla Tincture

Vanilla, cut into small pieces	**100 g.**
Sucrose, in coarse granules	**200 g.**
Alcohol,	
Diluted Alcohol,	
Purified Water, each a sufficient quantity,	
To make	**1000 ml.**

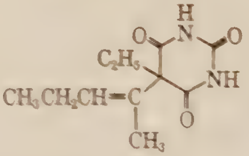
Add 200 ml. of water to the comminuted vanilla in a suitable covered container, and macerate during 12 hours, preferably in a warm place. Add 200 ml. of alcohol to the mixture of vanilla and water, mix well, and macerate for about 3 days. Transfer the mixture to a percolator containing the sucrose, and drain; then pack the drug firmly, and percolate slowly, using diluted alcohol as the menstruum.

Alcohol content, page 772—Vanilla Tincture contains from 38 to 42 percent (v/v) of C_2H_5OH.

Packaging and storage—Preserve Vanilla Tincture in tight, light-resistant containers and avoid exposure to direct sunlight or to excessive heat.

Category—Flavor.

Vinbarbital



5-Ethyl-5-(1-methyl-1-butenyl)barbituric Acid

$C_{11}H_{16}N_2O_3$ Mol. wt. 224.26

Vinbarbital, dried at 105° for 2 hours, contains not less than 98.5 percent and not more than 100.5 percent of $C_{11}H_{16}N_2O_3$.

Description—Vinbarbital occurs as a white powder. It has a characteristic odor and a bitter taste.

Solubility—Vinbarbital is very slightly soluble in water and is soluble in alcohol. It is sparingly soluble in ether.

Identification—

A: Boil about 200 mg. of Vinbarbital with 10 ml. of sodium hydroxide T.S.: ammonia is evolved.

B: Shake about 300 mg. of Vinbarbital for 2 minutes with 1 ml. of 1 *N* sodium hydroxide and 5 ml. of water, filter, and divide the filtrate into two portions. To one portion add mercuric nitrate T.S.: a white precipitate is formed which is soluble in ammonia T.S. To the other portion add silver nitrate T.S. a few drops at a time: a white precipitate is formed, which at first redissolves, but becomes insoluble when an excess of silver nitrate has been added.

Melting range, page 814—Vinbarbital melts between 160° and 163°.

Infrared absorption, page 866—The infrared absorption spectrum of a potassium bromide dispersion of Vinbarbital, previously dried at 105° for 2 hours, exhibits maxima only at the same wavelengths as that of NF Vinbarbital Reference Standard, similarly measured.

Ultraviolet absorption, page 866—The ultraviolet absorption spectrum of a 1 in 100,000 solution of Vinbarbital in 0.1 *N* sodium hydroxide exhibits maxima and minima at the same wavelengths as that of NF Vinbarbital Reference Standard, similarly measured, and the respective absorptivities, calculated on the dried basis, at the point of maximum absorbance occurring at about 252 $m\mu$, do not differ by more than 3 percent.

Loss on drying, page 814—Dry Vinbarbital at 105° for 2 hours: it loses not more than 1.5 percent of its weight.

Residue on ignition, page 858—Vinbarbital yields not more than 0.1 percent of residue on ignition.

Sulfate—To a 25-ml. portion of the solution prepared for the test for *Halide* add 1 ml. of barium nitrate T.S.: no turbidity is produced.

Halide—Digest 2 g. of Vinbarbital with 100 ml. of water at about 70° for 15 minutes, cool at once to 20°, and filter. To a 25-ml. portion add 0.5 ml. of silver nitrate T.S.: no opalescence is produced.

Heavy metals, page 806—Dissolve 500 mg. of Vinbarbital in a mixture of 5 ml. of sodium hydroxide T.S. and 20 ml. of water, and then add 5 drops of sodium sulfide T.S.: no color or precipitate is produced.

Assay—Dissolve about 500 mg. of Vinbarbital, previously dried at 105° for 2 hours and accurately weighed, in 25 ml. of alcohol, add 25 ml. of water and 3 drops of thymolphthalein T.S., and titrate to the first faint blue color with 0.1 *N* sodium hydroxide. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 22.43 mg. of $C_{11}H_{16}N_2O_3$.

Packaging and storage—Preserve Vinbarbital in tight containers.

CATEGORY—Sedative.

USUAL DOSE—**100** to **200** mg. at bedtime.

Vinbarbital Capsules

Vinbarbital Capsules contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{11}H_{16}N_2O_3$.

Identification—Macerate the contents of a sufficient number of Vinbarbital Capsules, equivalent to about 500 mg. of vinbarbital, with 15 ml. of warm alcohol for 20 minutes, filter, and evaporate the filtrate to dryness on a steam bath. A portion of the residue so obtained responds to the *Identification tests* and to the test for *Ultraviolet absorption* under *Vinbarbital,* page 756.

Weight variation, page 901—Vinbarbital Capsules meet the requirements of the weight variation test for capsules.

Assay—Transfer as completely as possible the contents of not less than 20 Vinbarbital Capsules to a 50-ml. volumetric flask. Place the emptied capsules in a small beaker, add 15 ml. of alcohol and allow to stand for 10 minutes, with frequent agitation. Filter into the volumetric flask, wash the beaker with 10 ml. of alcohol, and filter into the same flask. Dilute to volume with water, and mix. Transfer an accurately measured portion of the solution, equivalent to about 500 mg. of vinbarbital, to a conical flask, add 3 drops of thymolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to the first faint blue color. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* sodium hydroxide is equivalent to 22.43 mg. of $C_{11}H_{16}N_2O_3$.

Packaging and storage—Preserve Vinbarbital Capsules in tight containers.

Capsules available—Vinbarbital Capsules usually available contain the following amount of vinbarbital: 100 mg.

CATEGORY and DOSE—See Vinbarbital.

Vinbarbital, Sodium, Injection, page 662

Vinyl Ether

$CH_2{=}CH{-}O{-}CH{=}CH_2$

C_4H_6O Mol. wt. 70.09

Vinyl Ether contains from 96.0 percent to 97.0 percent of C_4H_6O, the remainder consisting of dehydrated alcohol. It may contain not more than 0.025 percent of a suitable preservative.

Caution: Do not use Vinyl Ether for anesthesia if the original container has been opened longer than 48 hours. It is flammable.

Description—Vinyl Ether is a clear liquid having a characteristic odor. It is colorless or has a slight purple fluorescence derived from the preservative. It boils at about 30°.

Solubility—Vinyl Ether is slightly soluble in water. It is miscible with alcohol, with acetone, with chloroform, and with ether.

Specific gravity, page 866—The specific gravity of Vinyl Ether is not less than 0.767 and not more than 0.771.

Reaction—Agitate 5 ml. of Vinyl Ether in a small, stoppered cylinder with 2 ml. of carbon dioxide-free water for 30 seconds: the water layer is neutral to litmus.

Nonvolatile residue—Allow 10 ml. of Vinyl Ether to evaporate at room temperature in a tared evaporating dish, and dry the residue at 105° for 1 hour: the weight of the residue does not exceed 2 mg. (0.03 percent).

Foreign odor—Place 10 ml. of Vinyl Ether in a dry, small evaporating dish, and allow it to evaporate spontaneously to about 1 ml.: no foreign odor is perceptible during the evaporation. Pour the residue onto odorless filter paper: no foreign odor other than that of alcohol is perceptible as the last portions disappear from the paper.

Aldehyde—To 5 ml. of Vinyl Ether, contained in a glass-stoppered, 10-ml. cylinder, add 1 ml. of a freshly prepared alkaline solution of phloroglucinol (made by dissolving 20 mg. of phloroglucinol in 4 ml. of sodium hydroxide solution [1 in 10] and diluting with water to 50 ml.), stopper the cylinder, and shake it vigorously for 3 minutes: upon separation the lower layer is not darker than a control made with 5 ml. of benzene and 1 ml. of the phloroglucinol solution.

Chlorine—In one hole of a rubber stopper insert a small separator. Into another hole insert a glass tube of such length that when the stopper is inserted into a small suction flask the lower end of the tube will be about 1 cm. from the bottom of the flask. Connect this tube with a source of illuminating gas, and connect the side arm of the suction flask to a Bunsen burner placed at a safe distance from the flask. Start the flow of the illuminating gas, and light the burner. Then introduce through the separator, dropwise, 5 ml. of Vinyl Ether. Allow the flame from the Bunsen burner to impinge on a clean, previously ignited, heavy copper gauze: when viewed in a dark room or against a black background, no green color is perceptible above the gauze.

Packaging and storage—Preserve Vinyl Ether in tight, light-resistant containers of not more than 200-ml. capacity and do not store at temperatures exceeding 26°.

CATEGORY—General anesthetic.

APPLICATION—By inhalation as required.

Vitamin E

Vitamin E is a suitable form of alpha tocopherol ($C_{29}H_{50}O_2$). It may consist of *d*- or *dl*-alpha tocopherol ($C_{29}H_{50}O_2$), *d*- or *dl*-alpha tocopheryl acetate ($C_{31}H_{52}O_3$), *d*- or *dl*-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$), mixed tocopherols concentrate, or *d*-alpha tocopheryl acetate concentrate. The concentrates are obtained from edible vegetable oils or from the by-products of their refining.

d- or *dl*-Alpha tocopherol, *d*- or *dl*-alpha tocopheryl acetate, and *d*- or *dl*-alpha tocopheryl acid succinate contain not less than 97.0 percent and not more than 100.5 percent of $C_{29}H_{50}O_2$, $C_{31}H_{52}O_3$, or $C_{33}H_{54}O_5$, respectively.

Mixed tocopherols concentrate contains not less than 34.0 percent of total tocopherols and may be so adjusted by the addition of an edible vegetable oil. Of the total tocopherols present, not less than 50.0 percent consists of *d*-alpha tocopherol, the content of which may be adjusted by physical or chemical means.

d-Alpha tocopheryl acetate concentrate contains not less than 25.0 percent of *d*-alpha tocopheryl acetate and may be so adjusted by the addition of an edible vegetable oil. Of the total tocopheryl acetates present, not less than 64.0 percent consists of *d*-alpha tocopheryl acetate, the content of which may be adjusted by physical or chemical means.

Description—Vitamin E has little or no odor or taste. The alpha tocopherols and alpha tocopheryl acetates occur as clear, yellow, viscous oils. *d*-Alpha tocopheryl acetate may solidify in the cold. Alpha tocopheryl acid succinate occurs as a white powder; the *d*-isomer melts within the range of about 73° to 78°, and the *dl*-isomer melts within the range of about 68° to 74°. The concentrates occur as clear, yellow to brownish-red, viscous oils. The esters are stable to air and to light but are unstable to alkali; the acid succinate is also unstable when held molten. The alpha tocopherols are unstable to air and to light, particularly when in alkaline media.

Solubility—Alpha tocopheryl acid succinate is insoluble in water; slightly soluble in alkaline solutions; soluble in alcohol, ether, acetone, and vegetable oils; and very soluble in chloroform. The other forms of Vitamin E are insoluble in water; soluble in alcohol; and miscible with ether, acetone, vegetable oils, and chloroform.

Identification—

A: Prepare a solution in dehydrated alcohol of unesterified alpha tocopherol, or use an aliquot of the residue from hydrolysis of the esters, containing about 10 mg. of tocopherols in each 10 ml. Add, with swirling, 2 ml. of nitric acid, and heat at about 75° for 15 minutes: a bright red or orange color develops.

B: If not otherwise known, the isomeric form in which the Vitamin E occurs may be determined as follows: (a) The *dl* forms, dissolved in chloroform to make a 1 in 10 solution, show no appreciable angular rotation. (b) For the *d* forms, prepare a solution of about 100 mg. of unesterified alpha tocopherol in 50 ml. of ether, or in the case of esterified *d*-tocopherols, place an aliquot from the hydrolysis of the esters containing about 100 mg. of the sample in a separator and add 75 ml. of water. Extract with two 25-ml. portions of ether, and combine the ether extracts in another separator. To the ether solution of unesterified or hydrolyzed alpha tocopherol, add 20 ml. of a 1 in 10 solution of potassium ferricyanide in 0.2 *N* sodium hydroxide, and shake for 3 minutes. Wash the ether solution with four 50-ml. portions of water, and discard the washings. Evaporate the ether solution on a water bath under reduced pressure or in an atmosphere of nitrogen until about 7 or 8 ml. remain, and then complete the evaporation to dryness, removing the last traces of ether, without the application of heat. Immediately dissolve the residue in 5.0 ml. of isooctane, and determine the optical rotation in a 2-decimeter tube. Calculate the specific rotation (see page 822), using as *c* the number of g. of total tocopherols, determined in the *Assay*, in each 100 ml. of solution employed for the test: the *d*-isomers have a specific rotation of not less than +15°.

Acidity—Dissolve 1 g. of the sample in 25 ml. of a mixture of equal volumes of alcohol and ether (which has been neutralized to phenolphthalein with 0.1 *N* sodium hydroxide), add 0.5 ml. of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide until the solution remains faintly pink after shaking for 30 seconds: alpha tocopheryl acid succinate requires not less than 18.0 ml. and not more than 19.3 ml. of 0.1 *N* sodium hydroxide; the other forms of Vitamin E require not more than 1.0 ml. of 0.1 *N* sodium hydroxide.

Assay—

Assay preparation for alpha tocopheryl acetate—Transfer about 220 mg. of the sample, accurately weighed, to a light-resistant, round-bottom, glass-stoppered 150-ml. flask, dissolve in 25 ml. of dehydrated alcohol, and add 20 ml. of 5 *N* alcoholic sulfuric acid. Reflux in all-glass apparatus for 3 hours, protected from sunlight. Cool to room temperature, transfer quantitatively to a 200-ml. light-resistant volumetric flask, dilute to volume with 0.5 *N* alcoholic sulfuric acid, and mix.

Assay preparation for alpha tocopheryl acid succinate and for alpha tocopheryl acetate concentrate—Transfer an accurately weighed amount of the sample, equivalent to about 200 mg. of total tocopherols, to a light-resistant, round-bottom, glass-stoppered 250-ml. flask, dissolve in 50 ml. of dehydrated alcohol, and reflux for 1 minute. While the solution is boiling, add through the condenser 1 g. of potassium hydroxide pellets, one at a time to avoid overheating. (*Caution: Wear safety goggles.*) Continue refluxing for 20 minutes, and without cooling add, dropwise, 2 ml. of hydrochloric acid through the condenser. [Note—This technique is essential to prevent oxidative action by air while the sample is in alkaline medium.] Cool to room temperature, and transfer the contents of the flask to a light-resistant 500-ml. separator, rinsing the flask with 100 ml. each of water and of ether. Shake vigorously, allow the layers to separate, and collect each of the two layers in separate flasks. Extract the water layer with two 50-ml. portions of ether, and add these extracts to the first ether extract. Wash the combined ether extracts with four 100-ml. portions of water, and then evaporate the ether solution on a water bath under reduced pressure or in an atmosphere of nitrogen until about 7 or 8 ml. of liquid remain. Complete the evaporation to dryness, removing the last traces of ether, without application of heat. If the sample is *d*- or *dl*-alpha tocopheryl acid succinate, immediately dissolve the residue in 0.5 *N* alcoholic sulfuric acid, add sufficient 0.5 *N* alcoholic sulfuric acid to make 200.0 ml., and mix. If the sample is alpha tocopheryl acetate concentrate, immediately dissolve the residue in dehydrated alcohol, add sufficient dehydrated alcohol to make 250.0 ml., and mix. Express the concentration of the *Assay preparations* in terms of the number of g. of the original sample, *before hydrolysis,* in each 100 ml. of the final solution.

Assay preparation for mixed tocopherols concentrate—Dissolve an accurately weighed amount of the sample, equivalent to about 15 mg. of total tocopherols, in sufficient dehydrated alcohol to make 100.0 ml.

Assay preparation for alpha tocopherol—Dissolve about 100 mg. of the sample, accurately weighed, in sufficient 0.5 *N* alcoholic sulfuric acid to make 100.0 ml.

Procedure for alpha tocopherol, alpha tocopheryl acetate, and for alpha tocopheryl acid succinate—Transfer to a 250-ml. conical flask 50.0 ml. of the *Assay preparation for alpha tocopherol,* or of the *Assay preparation for alpha tocopheryl acetate,* or of the *Assay preparation for alpha tocopheryl acid succinate.* Add 50 ml. of 0.5 *N* alcoholic sulfuric acid, 20 ml. of water, and 2 drops of diphenylamine T.S., and titrate with 0.01 *N* ceric sulfate at a rate of approximately 25 drops per 10 seconds, swirling or stirring constantly, until a blue end-point is reached which persists for 10 seconds. Perform a blank determination using 100 ml. of 0.5 *N* alcoholic sulfuric acid, and make any necessary correction. Each ml. of 0.01 *N* ceric sulfate is equivalent to 2.154 mg. of *d*- or *dl*-alpha tocopherol ($C_{29}H_{50}O_2$), or to 2.364 mg. of *d*- or *dl*-alpha tocopheryl acetate ($C_{31}H_{52}O_3$), or to 2.654 mg. of *d*- or *dl*-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$).

Procedure for alpha tocopheryl acetate concentrate—

TOTAL TOCOPHERYL ACETATES*—Transfer an accurately measured volume of the *Assay preparation for alpha tocopheryl acetate concentrate,* equivalent to about 15 mg. of total tocopherols, to a 100-ml. volumetric flask, dilute to volume with dehydrated alcohol, and mix. This is the *diluted Assay preparation.* Transfer 2.0 ml. of the *diluted Assay preparation* to an opaque glass-stoppered flask, and transfer 2.0 ml. of dehydrated alcohol to a second flask to serve as the blank. To each flask add 1.0 ml. of a solution of ferric chloride in dehydrated alcohol (1 in 500), and begin timing the reaction, preferably with a stopwatch. Immediately add 1.0 ml. of a solution of 2,2′-bipyridine in dehydrated alcohol (1 in 200), mix thoroughly by swirling, then add 21.0 ml. of dehydrated alcohol, and shake vigorously to ensure complete mixing. Exactly 10 minutes after addition of the ferric chloride solution, determine the absorbance of the solutions in 1-cm. cells, at 520 mμ, with a suitable spectrophotometer, using dehydrated alcohol to set the instrument. Subtract the absorbance of the blank from that of the sample solution, and record the difference as A_D. Calculate the quantity, in mg., of total tocopherols in each g. of the sample by the formula 29.2 A_D/C_D, in which 29.2 is a factor derived from data on *alpha-*, *beta-*, *gamma-*, and *delta-*tocopherols present in alpha tocopheryl acetate concentrate, and C_D is the concentration, in g. per 100 ml., of the *diluted Assay preparation.* Multiply the value so obtained by 1.098 to obtain the mg. of total tocopheryl acetates.

NONALPHA TOCOPHERYL ACETATES—(NOTE: Adjust all glassware and reagents to 25 ± 1° by immersing in a water bath adjusted to this temperature.) Transfer an accurately measured volume of the *Assay preparation for alpha tocopheryl acetate concentrate,* equivalent to about 15 mg. of nonalpha tocopherols, to a 100-ml. volumetric flask, dilute to volume with dehydrated alcohol, and mix. This is the *diluted Assay preparation.* Transfer 5.0 ml. of the *diluted Assay preparation* to a glass-stoppered 50-ml. cylinder, and transfer 5.0 ml. of dehydrated alcohol to a second cylinder to serve as the blank. To each cylinder add 0.2 ml. of glacial acetic acid, and mix thoroughly by swirling. Add 3 ml. of a freshly prepared solution of sodium nitrite (1 in 50) from a rapid-delivery pipet, swirling vigorously for 5 seconds, and then allow to stand for exactly 1 minute in the 25 ± 1° water bath. Add 2 ml. of potassium hydroxide solution (1 in 5), mix thoroughly, and then add 10 ml. of water, 200 mg. of anhydrous sodium sulfate, and 12.0 ml. of solvent hexane. Stopper the cylinder, shake vigorously for 30 seconds, and allow the layers to separate. Transfer a portion of the upper layer from each cylinder to a 1-cm. cell, and determine the absorbance at 410 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance as A_N. Calculate the quantity, in mg., of nonalpha tocopherols in each g. of the sample by the formula $47.3A_N/C_N$, in which 47.3 is a factor derived from data on *beta-*, *gamma-*, and *delta*-tocopherols in alpha tocopheryl acetate concentrate, and C_N is the concentration, in g. per 100 ml., of the *diluted Assay preparation*. Multiply the value so obtained by 1.098 to obtain the mg. of nonalpha tocopheryl acetates.

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*NOTE: The absorbance of the blank can sometimes be reduced, and the precision of the determination thereby improved, by purification of the dehydrated alcohol. Purification may be accomplished by adding 0.01 to 0.02 percent of potassium permanganate and of potassium hydroxide to the dehydrated alcohol and redistilling.

CALCULATION—Calculate the *d*-alpha tocopheryl acetate content, in mg., of *d*-alpha tocopheryl acetate concentrate by subtracting the mg. of nonalpha tocopheryl acetates from the mg. of total tocopheryl acetates.

Procedure for mixed tocopherols concentrate—

TOTAL TOCOPHEROLS—Transfer 2.0 ml. of the *Assay preparation for mixed tocopherols concentrate* to an opaque glass-stoppered flask, transfer 2.0 ml. of dehydrated alcohol to a second flask to serve as the blank, and continue as directed for *Total tocopheryl acetates* under *Procedure for alpha tocopheryl acetate concentrate*, beginning with "To each flask add 1.0 ml. of a solution of ferric chloride in dehydrated alcohol. . . ." Calculate the quantity, in mg., of total tocopherols in each g. of the sample by the formula $28.2A_D/C_D$, in which 28.2 is a factor derived from data on *alpha-*, *beta-*, *gamma-*, and *delta*-tocopherols present in mixed tocopherols concentrate, and C_D is the concentration, in g. per 100 ml., of the *Assay preparation*.

NONALPHA TOCOPHEROLS—Transfer 5.0 ml. of the *Assay preparation for mixed tocopherols concentrate* to a glass-stoppered 50-ml. cylinder, transfer 5.0 ml. of dehydrated alcohol to a second cylinder to serve as the blank, and continue as directed for *Nonalpha tocopheryl acetates* under *Procedure for alpha tocopheryl acetate concentrate*, beginning with "To each cylinder add 0.2 ml. of glacial acetic acid. . . ." Calculate the quantity, in mg., of nonalpha tocopherols in each g. of the sample by the formula $40.8A_N/C_N$, in which 40.8 is a factor derived from data on *beta-*, *gamma-*, and *delta*-tocopherols in mixed tocopherols concentrate, and C_N is the concentration, in g. per 100 ml., of the *Assay preparation*.

CALCULATION—Calculate the *d*-alpha tocopherol content, in mg., of mixed tocopherols concentrate by subtracting the mg. of nonalpha tocopherols from the mg. of total tocopherols.

Packaging and storage—Preserve Vitamin E in tight containers, protected from light.

Labeling—Label Vitamin E to indicate the chemical form present. Each form of Vitamin E is also labeled in terms of the mg. of the chemical entity, or its equivalent in terms of International Units of Vitamin E (see page 905). Label alpha tocopherol and its esters to indicate whether they are *d* or *dl*. Mixed tocopherols concentrate may be labeled in terms of mg. of mixed tocopherols, provided it is also labeled in terms of mg. of *d*-alpha tocopherol or its equivalent in International Units of Vitamin E.

CATEGORY—Vitamin E supplement.

USUAL DOSE RANGE—Prophylactic: from 5 to 30 International Units of Vitamin E (see page 905); Therapeutic: to be determined by the physician according to the needs of the patient.

Warfarin, Potassium, page 578
Warfarin, Potassium, Tablets, page 579

Yellow Wax

Yellow Wax is the purified wax from the honeycomb of the bee, *Apis mellifera* Linné (Fam. *Apidæ*).

Description—Yellow Wax is a solid, varying in color from yellow to grayish brown. It has an agreeable, honey-like odor. It is somewhat brittle when cold, and presents a dull, granular, noncrystalline fracture when broken. It becomes pliable from the heat of the hand. Its specific gravity is about 0.95.

Solubility—Yellow Wax is insoluble in water, and sparingly soluble in cold alcohol. Boiling alcohol dissolves the cerotic acid and a portion of the myricin, which are constituents of Yellow Wax. Yellow Wax is completely soluble in chloroform, in ether, and in fixed and volatile oils. It is partly soluble in cold benzene and in cold carbon disulfide, and is completely soluble in these liquids at about 30°.

Melting range, *Class II*, page 814—Yellow Wax melts between 62° and 65°.

Carnauba wax—Place 100 mg. of Yellow Wax in a test tube, and add 20 ml. of *n*-butanol. Immerse the test tube in boiling water, and shake the mixture gently until solution is complete. Immerse the test tube in a beaker of water at 60°, and allow it to cool to room temperature. A loose mass of fine, needle-like crystals separates from a clear mother-liquor. Under the microscope the crystals appear as loose needles or stellate clusters: the presence of amorphous masses indicates the presence of carnauba wax.

Saponification cloud test—Place 3.00 g. of Yellow Wax in a round-bottom, 100-ml. boiling flask fitted with a ground-glass joint and a reflux condenser. Add 30 ml. of 0.5 *N* alcoholic potassium hydroxide (prepared without water), and reflux the mixture gently for 2 hours. At the end of this period, open the flask, insert a thermometer into the solution, and place the flask in a container of water at a temperature of 80°. Rotate the flask in the bath while both the bath and the solution cool: the solution shows no cloudiness or globule formation before the temperature reaches 65°.

Fats or fatty acids, Japan wax, rosin, and soap—Boil 1 g. of Yellow Wax for 30 minutes with 35 ml. of sodium hydroxide solution (1 in 7) contained in a 100-ml. beaker, maintaining the volume by the occasional addition of water, and allow the mixture to cool at room temperature for about 2 hours: the wax separates leaving the liquid clear, turbid, or translucent, but not opaque. Filter the cool mixture, and acidify the clear filtrate with hydrochloric acid: the liquid remains clear or shows not more than a slight amount of turbidity or precipitate.

Acid value, page 804—Warm about 3 g. of Yellow Wax, accurately weighed, in a 200-ml. flask with 25 ml. of neutralized dehydrated alcohol until melted, shake the mixture, add 1 ml. of phenolphthalein T.S., and titrate the warm liquid with 0.5 *N* alcoholic potassium hydroxide to produce a permanent, faint pink color: the acid value so obtained is not less than 18 and not more than 24.

Ester value, page 804—To the solution resulting from the determination of *Acid value* add 25.0 ml. of 0.5 *N* alcoholic potassium hydroxide and 50 ml. of alcohol, boil the mixture for 4 hours under a reflux condenser, and titrate the excess alkali with 0.5 *N* hydrochloric acid. Perform a blank determination (see *Residual Titrations,* page 883). The ester value so obtained is not less than 72 and not more than 77.

Packaging and storage—Preserve Yellow Wax in well-closed containers.

CATEGORY—Stiffening agent.

White Lotion

Zinc Sulfate	**40 g.**
Sulfurated Potash	**40 g.**
Purified Water, a sufficient quantity to make	**1000 ml.**

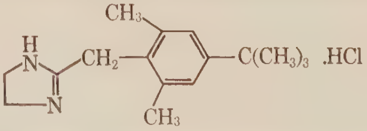
Dissolve the zinc sulfate and the sulfurated potash separately, each in 450 ml. of purified water, and filter each solution. Add the sulfurated potash solution slowly to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

NOTE—Prepare the Lotion freshly and shake thoroughly before dispensing.

CATEGORY—Local astringent and protectant.

FOR EXTERNAL USE—Topically, as required.

Xylometazoline Hydrochloride*



2-(4-*tert*-Butyl-2,6-dimethylbenzyl)-2-imidazoline Monohydrochloride

$C_{16}H_{24}N_2 . HCl$ Mol. wt. 280.84

Xylometazoline Hydrochloride contains not less than 99.0 percent and not more than 100.5 percent of $C_{16}H_{24}N_2 . HCl$, calculated on the dried basis.

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* Patented. See notice, page ii.

Description—Xylometazoline Hydrochloride occurs as a white, odorless, crystalline powder. It melts above 300° with decomposition.

Solubility—Xylometazoline Hydrochloride is soluble in water. It is freely soluble in alcohol, sparingly soluble in chloroform, and practically insoluble in benzene and in ether.

Identification—Dissolve about 25 mg. of Xylometazoline Hydrochloride in 50 ml. of water. To 1 ml. of this solution add 0.5 ml. of sodium nitroferricyanide T.S. and 0.5 ml. of 0.5 *M* sodium hydroxide. After 10 minutes, add 1 ml. of 1 *M* sodium bicarbonate solution, and dilute to 10 ml. with water: a violet color is produced.

Infrared absorption, page 866—The infrared absorption spectrum of a mineral oil dispersion of Xylometazoline Hydrochloride, previously dried at 105° for 4 hours, exhibits maxima only at the same wavelengths as that of NF Xylometazoline Hydrochloride Reference Standard, similarly measured.

pH, page 824—The pH of a solution of Xylometazoline Hydrochloride (1 in 20) is between 4.5 and 5.5.

Loss on drying, page 814—Dry Xylometazoline Hydrochloride at 105° for 4 hours: it loses not more than 0.5 percent of its weight.

Residue on ignition, page 858—Xylometazoline Hydrochloride yields not more than 0.1 percent of residue on ignition.

Heavy metals, *Method II*, page 806—The heavy metals limit for Xylometazoline Hydrochloride is 20 parts per million.

Iron—Dissolve 1 g. of Xylometazoline Hydrochloride in 40 ml. of water in a color comparison tube, add 2 ml. of hydrochloric acid, 50 mg. of ammonium persulfate, and 3 ml. of 1 *N* ammonium thiocyanate, and dilute to 50 ml. with water. To a similar tube add 2 ml. of hydrochloric acid, 5 ml. of freshly prepared standard iron solution (0.01 mg. Fe per ml.), 50 mg. of ammonium persulfate, and 3 ml. of 1 *N* ammonium thiocyanate, and dilute to 50 ml. with water. Mix both tubes, and compare the colors: the color of the sample solution is no darker than that of the iron standard (50 parts per million Fe).

Sulfate, page 784—One g. of Xylometazoline Hydrochloride shows no more sulfate than corresponds to 0.2 ml. of 0.02 *N* sulfuric acid (0.02 percent).

Assay—Dissolve about 500 mg. of Xylometazoline Hydrochloride in 70 ml. of glacial acetic acid, add 60 ml. of mercuric acetate T.S. and 7 drops of *p*-naphtholbenzein T.S., and titrate with 0.1 *N* perchloric acid in glacial acetic acid to a green end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* perchloric acid is equivalent to 28.08 mg. of $C_{16}H_{24}N_2 . HCl$.

Packaging and storage—Preserve Xylometazoline Hydrochloride in tight, light-resistant containers.

CATEGORY—Adrenergic (vasoconstrictor).

APPLICATION—Nasally, 2 or 3 drops of a 0.05 percent or 0.1 percent solution every 4 to 6 hours.

Xylometazoline Hydrochloride Solution

Xylometazoline Hydrochloride Solution is a solution of xylometazoline hydrochloride in water adjusted to a suitable pH and tonicity. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{16}H_{24}N_2 . HCl$.

Identification—Transfer a volume of Xylometazoline Hydrochloride Solution, equivalent to about 2.5 mg. of xylometazoline hydrochloride, to a 60-ml. separator containing 25 ml. of sodium hydroxide T.S., and extract with three 10-ml. portions of chloroform, filtering each extract through cotton into a 150-ml. beaker. Evaporate the filtrate to dryness on a steam bath, and dissolve the residue in 5 ml. of glacial acetic acid. Add 5 ml. of water and 1 ml. of a saturated solution of sodium nitrite, and heat in a water bath at 60° for 10 minutes. Add 10 ml. of ammonium sulfamate solution (1 in 10), mix, and transfer the solution to a polarographic cell. Deaerate by bubbling purified nitrogen through the solution for 10 minutes. Insert the dropping mercury electrode of a suitable polarograph, and record the polarogram from -0.25 to -1.25 volts, using a saturated calomel electrode as the reference electrode: the polarogram exhibits a half-wave potential within 1 percent of that of NF Xylometazoline Hydrochloride Reference Standard, treated in the same manner as the sample and similarly measured.

Assay—

Standard preparation—Transfer about 50 mg. of NF Xylometazoline Hydrochloride Reference Standard, accurately weighed, to a 100-ml. volumetric flask, add water to volume, and mix. Transfer 5.0 ml. of this solution to a 125-ml. separator, and continue as directed under *Assay preparation*, beginning with "... add 10 ml. each of water and of 2 *N* hydrochloric acid, and extract. ..."

Assay preparation—Transfer an accurately measured volume of Xylometazoline Hydrochloride Solution, equivalent to about 2.5 mg. of xylometazoline hydrochloride, to a 125-ml. separator, add 10 ml. each of water and of 2 *N* hydrochloric acid, and extract with three 10-ml. portions of methylene chloride. Discard the methylene chloride extracts, add 10 ml. of 5 *N* sodium hydroxide to the separator, and extract with five 10-ml. portions of methylene chloride. Filter the combined extracts through glass wool into a 50-ml. volumetric flask, dilute to volume with methylene chloride, and mix.

Procedure—Transfer 20.0 ml. each of the *Standard preparation* and of the *Assay preparation* to separate 25-ml. volumetric flasks, and evaporate to dryness using gentle heat. Dissolve the residue in each flask in 1.0 ml. of methanol, and add 1.0 ml. of methanol to a third 25-ml. volumetric flask to serve as the blank. To each flask add 2 ml. of sodium nitroferricyanide T.S. and 1.0 ml. of 0.5 *N* sodium hydroxide, and shake mechanically for 45 minutes. Add 1.0 ml. of a saturated solution of sodium bicarbonate, shake mechanically for 10 minutes, dilute to volume with water, and mix. Concomitantly determine the absorbances of the solutions, in 1-cm. cells, at the maximum at about 560 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard preparation* as A_S and that from the *Assay preparation* as A_U. Calculate the quantity, in mg., of $C_{16}H_{24}N_2.HCl$ in each ml. of the Solution taken by the formula $0.05 \times (C/V) \times (A_U/A_S)$, in which C is the exact concentration, in mcg. per ml., of the *Standard preparation*, and V is the volume, in ml., of the Solution taken.

Packaging and storage—Preserve Xylometazoline Hydrochloride Solution in tight, light-resistant containers.

Solutions available—Xylometazoline Hydrochloride Solution usually available contains the following amounts of xylometazoline hydrochloride: 0.05 percent or 0.1 percent.

CATEGORY and APPLICATION—See Xylometazoline Hydrochloride.

Dried Yeast

Dried Yeast consists of the dried cells of any suitable strain of *Saccharomyces cerevisiæ* Meyan (Fam. *Saccharomycetaceæ*) or *Candida utilis* (Hanneberg) Lodder and Kreger-Van Rij (Fam. *Cryptococcaceæ*), commonly called Torula Yeast. Dried Yeast may be obtained by growing suitable strains of the above species in media other than those required for beer production using appropriate environmental conditions. Such yeasts, properly designated as to species, are commonly known as "Primary Dried Yeasts." Dried Yeast may also be obtained as a by-product from the brewing of beer. Such yeasts are washed free of beer residues prior to drying. The washing step may include one or more alkaline washes for the purpose of removing the insoluble acetic bitter resins deposited on the yeast cells from the hops. These yeasts are commonly known, respectively, as "Brewer's Dried Yeast" and "Debittered Brewer's Dried Yeast."

Dried Yeast contains not less than 45.0 percent of protein, and, in each g., the equivalent of not less than 300 mcg. of niacin, 40 mcg. of riboflavin, and 120 mcg. of thiamine hydrochloride.

Description—Dried Yeast occurs as yellowish white to weak yellowish orange flakes, granules, or powder, with an odor and taste characteristic of the type. Dried Yeast is inactive in fermenting power.

Histology—Dried Yeast, when examined under the microscope in water mounts, shows numerous irregular masses and isolated yeast cells, the latter ovate, elliptical, spheroidal, or elliptic-elongate in shape, some with one or more attached buds; up to 12 μ in length and up to 7.5 μ in width; each with a wall of fungous cellulose surrounding a protoplast containing refractile glycogen vacuoles and oil globules; occasional septate hyphal outgrowths of *Saccharomyces cerevisiæ* and segments of elongated forms of yeast films.

Fillers—Dried Yeast contains no starch, corn meal, or other filler, as determined microscopically.

Bacterial and mold count—Suspend Dried Yeast in sterile water, plate it on nutrient agar, and incubate it at 37.5° for 48 hours: the live bacteria count does not exceed 7500 per g. and the mold count does not exceed 50 per g.

Loss on drying, page 814—Dry Dried Yeast at 100° for 5 hours: it loses not more than 7 percent of its weight.

Ash—Proceed as directed for *Total Ash,* page 885. Dried Yeast yields not more than 8 percent of ash.

Salmonella, page 862—The test for *Salmonella* in Dried Yeast is negative.

Assay for niacin—Proceed as directed under *Niacin or Niacinamide Assay, Chemical Method,* page 818, using *Standard Niacin Preparation* as the *Standard Preparation* in the *Assay Procedure,* and the following as the *Sample Preparation:* Transfer to a suitable flask an accurately weighed portion of Dried Yeast, equivalent to about 500 mcg. of niacin, add 20 ml. of 1 *N* sulfuric acid, agitate vigorously, and wash down the sides of the flask with 1 *N* sulfuric acid. Heat the mixture in an autoclave at 121° to 123° for 30 minutes, and cool. If lumping occurs, agitate the mixture until the particles are evenly dispersed. Adjust to pH 6.8 with sodium hydroxide T.S., transfer to a 100-ml. volumetric flask, add water to volume, and mix. Filter before use if the solution is not clear.

Assay for protein—Using about 1 g. of Dried Yeast, accurately weighed, proceed as directed under *Nitrogen Determination —Method I,* page 821. The quantity of nitrogen so obtained, multiplied by 6.25, represents the equivalent weight of protein in the portion of Dried Yeast taken.

Assay for riboflavin—Using about 2 g. of Dried Yeast, accurately weighed, proceed as directed under *Riboflavin Assay,* page 859.

Assay for thiamine—Transfer to a suitable vessel about 2 g. of Dried Yeast, accurately weighed, add 20 ml. of 0.2 *N* hydrochloric acid, and mix thoroughly. Wash down the sides of the container with a small quantity of 0.2 *N* hydrochloric acid, and heat in an autoclave at 121° to 123° for 30 minutes. Cool, and disperse any clumped aggregates of solid. Transfer to a 100-ml. volumetric flask, and add water to volume. Transfer an aliquot of this solution, equivalent to approximately 20 mcg. of thiamine hydrochloride, to a 100-ml. centrifuge tube. Adjust to pH 4 to 4.5 with 2 *M* sodium acetate solution, using bromocresol green as an external indicator. Add 5 ml. of a 10 percent solution or suspension of a suitable diastatic enzyme preparation, and heat at 45° to 50° for 3 hours. Cool, clarify the mixture by centrifuging, and quantitatively transfer the supernatant liquid to a 100-ml. volumetric flask. Wash the residue with a 10-ml. and then with a 5-ml. portion of 0.1 *N* sulfuric acid, centrifuging each time and adding the washing to the main extract. Add water to volume, and mix. Using this solution as the *Assay Preparation,* proceed as directed under *Thiamine Assay,* page 881.

Packaging and storage—Preserve Dried Yeast in tight containers.

Labeling—Label Dried Yeast to indicate its source, as "Brewer's Dried Yeast," "Debittered Brewer's Dried Yeast," or "Primary Dried Yeast," whichever is appropriate. If prepared from a suitable strain of *Candida utilis* the labeling must identify the product as "Torula Dried Yeast."

CATEGORY—Natural source of protein and vitamin B-complex vitamins.

USUAL DOSE—**10 g.** four times a day.

Dried Yeast Tablets

Dried Yeast Tablets contain the equivalent of niacin, riboflavin, thiamine hydrochloride, and protein corresponding to not less than 95.0 percent of the labeled amount of dried yeast.

Disintegration, page 878—The disintegration time limit for Dried Yeast Tablets is 1 hour.

Weight variation, page 901—Dried Yeast Tablets meet the requirements of the weight variation test for tablets.

Salmonella, page 862—The test for *Salmonella* in Dried Yeast Tablets is negative.

Assay for niacin, riboflavin, and thiamine—Weigh and finely powder not less than 20 Dried Yeast Tablets, and proceed as directed in the *Assay for niacin, Assay for riboflavin,* and *Assay for thiamine* under *Dried Yeast,* page 764.

Assay for protein—Using about 1 g. of the powder, accurately weighed, proceed as directed under *Nitrogen Determination—Method I,* page 821. The quantity of nitrogen so obtained, multiplied by 6.25, represents the equivalent weight of protein in the portion of the powdered Dried Yeast Tablets taken.

Packaging and storage—Preserve Dried Yeast Tablets in tight containers.

Labeling—If the Tablets are prepared from *Torula Dried Yeast* this must be stated in the labeling.

Tablets available—Dried Yeast Tablets usually available contain the following amount of dried yeast: 500 mg.

CATEGORY and DOSE—See Dried Yeast.

Yellow Mercuric Oxide, page 415
Yellow Mercuric Oxide Ophthalmic Ointment, page 415
Yellow Ointment, page 496
Yellow Wax, page 761

Zinc-Eugenol Cement

1. The Powder

Zinc Acetate	**0.5 g.**
Zinc Stearate	**1 g.**
Zinc Oxide	**70 g.**
Rosin	**28.5 g.**

2. The Liquid

Eugenol	**85 ml.**
Cottonseed Oil	**15 ml.**

Powder the rosin and incorporate it with about an equal weight of zinc oxide until thoroughly mixed. Sift the mixture on a sieve of not less than 100-mesh. Regrind the material which does not pass through the sieve with more of the zinc oxide and sift again; repeat the process until all of the material readily passes through the sieve. Thoroughly mix the zinc stearate and zinc acetate with a portion of the zinc oxide and pass through a 100-mesh sieve. Thoroughly mix the two mixtures with the remainder of the zinc oxide.

Thoroughly mix the liquids together in the proportions specified.

To prepare the cement mix 10 parts of the Powder with 1 part of the Liquid to a thick paste immediately before use.

Note: The amount of Liquid may be varied to give any desired consistency.

The Powder

Description—The Powder is yellowish white to white in color.

Identification—

A: Mix 10 parts of the Powder with 1 part of the Liquid and transfer into a beaker containing water at 25°: the mixture hardens in not more than 20 minutes.

B: Triturate 1 g. of the Powder with 10 ml. of solvent hexane, filter the mixture, and to the filtrate add 10 ml. of a freshly prepared solution of cupric acetate (1 in 200), shake for a few minutes, and allow the liquid layers to separate: the solvent hexane layer is green in color.

C: The residue obtained in the *Assay for total zinc*, dissolved in a slight excess of hydrochloric acid, responds to the tests for *Zinc*, page 810.

D: Triturate 5 g. of the Powder with 25 ml. of water, filter, and to 10 ml. of the clear filtrate add 1 ml. of ferric chloride T.S. in a color comparison tube. Prepare a standard by adding 1 ml. of ferric chloride T.S. to 10 ml. of water in a matched color comparison tube: the color produced in the filtrate is a darker red than that produced in the standard when viewed downward against a white surface (*acetate*).

Assay for rosin—Place in a beaker 1 g. of the Powder, accurately weighed, add 50 ml. of chloroform, and stir for several minutes. Filter through a tared porcelain filtering crucible and completely transfer the insoluble material with additional portions of chloroform. Wash the crucible with chloroform, dry in an oven at 80°, cool and weigh: the loss in weight of the original sample is not less than 270 mg. and not more than 300 mg.

Assay for total zinc as zinc oxide—Ignite the residue obtained from the above *Assay for rosin* to constant weight, cool, and weigh: the weight of the ZnO so obtained is not less than 680 mg. and not more than 720 mg.

Packaging and storage—Preserve the Powder in well-closed containers.

The Liquid

Description—The Liquid is thin and colorless to weak yellow, having a strong aromatic odor of clove and a pungent, spicy taste. It is affected by light.

Solubility—The Liquid is miscible with alcohol, with chloroform, and with ether. It is only slightly soluble in water.

Identification—Shake 1 ml. of the Liquid with 20 ml. of water, filter, and add 1 drop of ferric chloride T.S. to 5 ml. of the clear filtrate: the mixture exhibits a transient pale yellow-green color.

Specific gravity, page 866—The specific gravity of the Liquid is not less than 1.043 and not more than 1.048.

Refractive index, page 866—The refractive index of the Liquid is not less than 1.528 and not more than 1.531 at 20°.

Packaging and storage—Preserve the Liquid in tight, light-resistant containers.

CATEGORY—Protective (dental).

Zinc Oxide Paste With Salicylic Acid

Zinc Oxide Paste with Salicylic Acid contains not less than 23.5 percent and not more than 25.5 percent, by weight, of ZnO (zinc oxide).

Salicylic Acid, in fine powder	**20 g.**
Zinc Oxide Paste, a sufficient quantity	
To make	**1000 g.**

Thoroughly triturate the salicylic acid with a portion of the paste; then add the remaining paste, and triturate until a smooth mixture is obtained.

Assay—Weigh accurately in a tared porcelain crucible about 500 mg. of Zinc Oxide Paste with Salicylic Acid, heat it gently until melted, and continue the heating, gradually raising the temperature until the mass is thoroughly charred. Ignite the mass strongly until all of the carbonaceous material has been dissipated and the residue is uniformly yellow and the weight is constant. The weight of the residue represents the quantity of ZnO in the weight of the Paste taken for the assay.

Packaging and storage—Preserve Zinc Oxide Paste with Salicylic Acid in well-closed containers.

CATEGORY—Astringent; local protective.

Zinc Undecylenate

$[CH_2{=}CHCH_2(CH_2)_6CH_2COO{-}]_2Zn$

Zinc 10-Undecenoate

$C_{22}H_{38}O_4Zn$ Mol. wt. 431.92

Zinc Undecylenate contains not less than 98.0 percent and not more than 102.0 percent of $C_{22}H_{38}O_4Zn$, calculated on the dried basis.

Description—Zinc Undecylenate occurs as a fine, white powder.

Solubility—Zinc Undecylenate is practically insoluble in water and in alcohol.

Identification—

A: Acidify about 5 g. of Zinc Undecylenate with 25 ml. of diluted sulfuric acid, add 20 ml. of water, and extract in a separator with two 25-ml. portions of ether. Evaporate the ether solution until there is no longer any odor of ether. Add potassium permanganate T.S. dropwise to a 1-ml. portion of this residue: the permanganate color is discharged.

B: Place a 3-ml. portion of the residue of undecylenic acid, obtained in *Identification test A*, and 3 ml. of freshly distilled aniline in a tall test tube, and heat for 10 minutes at a rate such that the ring of condensate remains just below the mouth of the tube. Cool, add 10 ml. of alcohol and 10 ml. of ether, and transfer to a separator. Wash the ether solution with four 20-ml. portions of water, and discard the water washings. Heat on a steam bath until the odor of ether is no longer perceptible, then add a few mg. of activated charcoal, mix well, and filter. Evaporate the filtrate nearly to dryness, and recrystallize the residue from 70 percent alcohol: the anilide so obtained melts between 66° and 67.5°, page 814.

C: Dissolve about 100 mg. of Zinc Undecylenate in 10 ml. of water and 1 ml. of stronger ammonia T.S., and add a few drops of sodium sulfide T.S.: a white, flocculent precipitate is formed.

Loss on drying, page 814—Dry Zinc

Undecylenate at 105° for 2 hours: it loses not more than 1.25 percent of its weight.

Alkalies and alkaline earths—Boil 1.5 g. of Zinc Undecylenate with 50 ml. of water and 10 ml. of hydrochloric acid, filter while hot, and wash the separated acid with about 50 ml. of hot water. Make the combined filtrate and washings alkaline with ammonia T.S., add ammonium sulfide T.S. to precipitate the zinc completely, dilute with water to 200 ml., mix well, and filter. To 100 ml. of the clear filtrate add 0.5 ml. of sulfuric acid, evaporate to dryness, and ignite to constant weight over a low flame: the weight of the residue does not exceed 7.5 mg. (1 percent).

Assay—Boil 50.0 ml. of 0.1 *N* sulfuric acid with about 1 g. of Zinc Undecylenate, accurately weighed, for 10 minutes, or until the undecylenic acid layer is clear, adding water, as necessary, to maintain the original volume. Cool, and transfer the mixture quantitatively, with the aid of water, to a 500-ml. separator. Dilute with water to about 250 ml., and extract with two 100-ml. portions of solvent hexane. Wash the combined extracts with water until the last washing is neutral to litmus, add the washings to the original water layer, and evaporate on a steam bath to about 100 ml. Cool, add 3 drops of methyl orange T.S., and titrate the excess sulfuric acid with 0.1 *N* sodium hydroxide. Perform a blank determination (see *Residual Titrations*, page 883). Each ml. of 0.1 *N* sulfuric acid is equivalent to 21.60 mg. of $C_{22}H_{38}O_4Zn$.

Packaging and storage—Preserve Zinc Undecylenate in well-closed containers.

CATEGORY—Local antifungal.

FOR EXTERNAL USE—Topically as a 20 percent ointment as required.

GENERAL TESTS, processes, techniques, and apparatus

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AEROSOLS

Delivery Rate—Select not less than 4 containers, remove the caps and covers, and actuate each for 2 to 3 seconds. Weigh each container accurately, and immerse in a constant-temperature bath until the internal pressure is equilibrated at a temperature of 25 ± 1° as determined by constancy of internal pressure as directed under *Pressure Testing*. Remove the containers from the bath, remove the excess moisture by blotting with a paper towel, actuate each container for 5.0 seconds (accurately timed by use of a stop-watch), and weigh each container again. Return the containers to the constant-temperature bath, and repeat the foregoing procedure three times for each container. Calculate the average delivery rate, in grams per second, for each container.

Leak Testing—Select 12 containers, and record the date and time to the nearest half-hour. Weigh each container to the nearest mg., and record the weight of each as W_1. Allow the containers to stand in an upright position for at least 3 days at room temperature, and then reweigh each container, recording the weight of each as

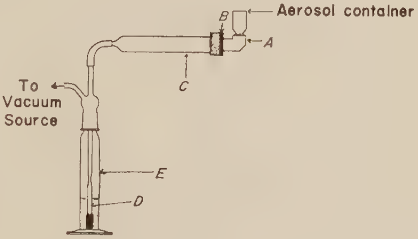
W_2 and recording the date and time to the nearest half-hour. Determine the time, T, in hours, during which the containers were under test. Calculate the leakage rate of each container, in mg. per year, by the formula $(W_1 - W_2) \times (365/T) \times (24)$.

The lot is acceptable if the average leakage rate of the 12 containers is not more than 3.5 percent of the labeled weight per year, and if none of the containers leaks more than 5.0 percent of the labeled weight per year. If 1 container leaks more than 5.0 percent per year, determine the leakage rate of an additional 24 containers as directed herein. The lot is acceptable if not more than 2 of the 36 containers leaks more than 5.0 percent of the labeled weight per year, and if none of the 36 containers leaks more than 7.0 percent of the labeled weight per year. This test is in addition to the customary in-line leak testing of each container.

Pressure Testing—Select not less than 4 containers, remove the caps and covers, and immerse in a constant-temperature bath until the internal pressure is constant at a temperature of 25 ± 1°. Remove the containers from the bath, shake well, and remove the actuator and water, if any, from the valve stem. Place each container in an upright position, and determine the pressure in each container by placing a prepressurized gauge on the valve stem, holding firmly and actuating the valve so that it is fully open. The gauge should be of a calibration approximating the expected pressure and should be fitted with an adapter appropriate for the particular valve stem dimensions. Read the pressure directly from the gauge.

Unit Spray Sampling Apparatus—The apparatus described herein is employed, where indicated in the individual monograph, to obtain a sample from metered-dose aerosol containers through the inhalation actuators provided.

The apparatus is illustrated in the accompanying diagram. It consists of an intake system, comprised of the inhalation actuator (A), intake adapter (B), and intake tube (C, approximately 5 × 15 cm., drawn to 8 mm. at one end); a delivery tube to which is attached a coarse-porosity sintered-glass dispersion bubbler (D); a collection chamber (E, gas-washing bottle) which contains an absorbing solution, and a vacuum system comprised of a vacuum source, a flow-regulator, and a flow meter. The intake adapter must be constructed to provide the necessary coupling to the inhalation actuator provided with the aerosol under test. The aerosol adapter has tapered inlet holes drilled through its center to provide an airtight seal and against which the aerosol valves can be actuated, delivering quantitatively their sprays into the intake tube. To avoid loss of the drug into the atmosphere when the self-pressurized unit is discharged, air is drawn continuously at the rate of 12 to 13 liters per minute through the intake system into the collection chamber and absorbing solution by means of a suitable vacuum system. Alternatively, an apparatus embodying the principle of the assembly described and illustrated may be used.



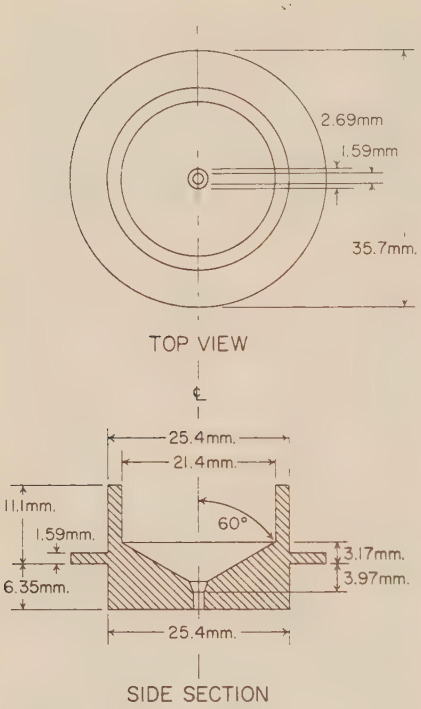
Sampling Apparatus for Metered-Dose Aerosols

Container Sampling Apparatus—The apparatus described herein is employed, where indicated in the individual monograph, to obtain a sample from metered-dose aerosol containers.

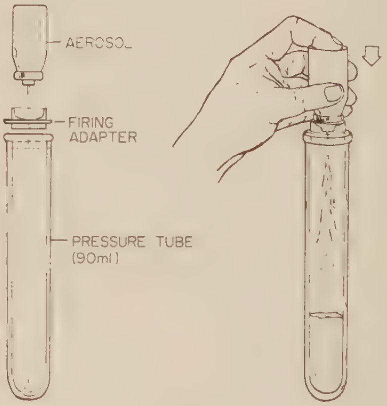
The apparatus, comprised of a pressure tube (compatability tube) and a pressure tube firing adapter, is illustrated in the accompanying diagram. The adapters are constructed to fit the mouth of the pressure tubes to provide a liquid-tight seal and have tapered inlet holes drilled through their centers to provide air-tight seats for the aerosol valve stems, against which the aerosol valves are actuated. Alternatively, an apparatus embodying the principles of the apparatus described and illustrated may be used.

Propellants—

General Sampling Procedure—This procedure is used to obtain samples for those propellants which occur as gases at about 25° and which are stored in pressurized cylinders. Use a stainless steel sample cylinder, equipped with a stainless steel valve, having a capacity of at least 200 ml. and a pressure rating of 240 p.s.i. or more. Dry the cylinder with the valve open at 110° for 2 hours, and then evacuate the hot cylinder to less than 1 mm. of mercury. Close the valve, cool, and weigh. Connect one end of a charging line tightly to the propellant container and the other end loosely to the sample cylinder. Carefully open the propellant container, and allow the propellant to flush out the charging line through the loose connection. Avoid excessive flushing that will cause moisture to freeze in the charging line and connections. Tighten the fitting on the sample cylinder, and open the sample cylinder valve, allowing the propellant to flow into the evacuated cylinder. Continue sampling until the



Pressure Tube Firing Adapter for Assay



Container Sampling Apparatus

desired amount of sample is obtained, then close the propellant container valve, and finally close the sample cylinder valve. (*Caution*—Do not overload the sample cylinder.) Reweigh the charged sample cylinder, and calculate the sample weight.

Approximate Boiling Temperature—Transfer a 100-ml. sample to a tared 100-ml. pear-shaped centrifuge tube containing a few boiling stones, and weigh. Suspend a suitable thermometer in the liquid, and place the tube in a medium maintained at a temperature 32 ± 1° above the expected boiling temperature. When the thermometer reading becomes constant, record as the boiling temperature the thermometer reading after 5 percent of the sample has distilled. Retain the remainder of the sample for the determination of *High-Boiling Residues*.

High-Boiling Residues—Allow 85 ml. of the sample to distil as directed in the test for *Approximate Boiling Temperature*, and then transfer the centrifuge tube containing the remaining 15 ml. of sample to a medium maintained at a temperature 10 ± 1° above the boiling temperature. After 30 minutes, remove the tube from the water bath, blot dry, and weigh. Calculate the weight of the residue.

Water Content—Proceed as directed under *Water Determination*, page 900, with the following modifications: (a) Provide the closed-system titrating vessel with an opening through which passes a coarse-porosity gas dispersion tube connected to a sampling cylinder. (b) Dilute the *Reagent* with anhydrous methanol to give a water equivalence factor of between 0.2 and 1.0 mg. per ml.; age this diluted solution at least 16 hours before standardization. (c) Obtain a 100-g. sample as directed under *General Sampling Procedure*, and introduce the sample into the titration vessel through the gas dispersion tube at a rate of about 100 ml. of gas per minute; if necessary, heat the sample cylinder gently to maintain this flow rate.

ALCOHOL DETERMINATION

Alcohol shall be determined by the *Distillation Procedure* unless otherwise stated in the individual monograph.

Distillation Procedure

General Procedure—By means of a pipet transfer to a suitable distilling apparatus not less than 25 ml., accurately measured, of the liquid in which the alcohol is to be determined, and note the temperature at which the volume was measured.

For Liquids Presumed to Contain Less than 30 Percent of Alcohol—Add an equal volume of water, distil, and collect a volume of distillate about 2 ml. less than the volume taken of the original test liquid, adjust to the temperature at which the original test liquid was measured, add sufficient water to measure exactly the original volume of the test liquid, and mix. The distillate is clear or not more than slightly cloudy, and does not contain more than traces of volatile substances other than alcohol and water. Determine the specific gravity of the liquid at 25°, as directed under *Specific Gravity*, page 866, using this result to ascertain the percentage, by volume, of alcohol contained in the liquid examined, by reference to the *Alcoholometric Table*, page 966.

For Liquids Presumed to Contain More than 30 Percent of Alcohol—Proceed as directed in the foregoing paragraph, except: dilute the sample with about twice its volume of water and collect a volume of distillate about 2 ml. less than twice the volume of the original test liquid, bring to the temperature at which the original liquid was measured, add sufficient water to measure exactly twice the original volume of the test liquid, mix, and determine its specific gravity. The proportion of alcohol, by volume, in this distillate, as ascertained from its specific gravity, equals one-half that in the liquid examined.

This general method is suitable for examining most fluidextracts and tinctures, provided the capacity of the distilling flask is sufficient (commonly two to four times the volume of the liquid to be distilled) and the rate of distillation is such that clear distillates are produced. Cloudy distillates may be clarified by agitation with talc, or with precipitated calcium carbonate, and filtered, after which the temperature of the filtrate is adjusted and the alcohol content determined from the specific gravity. During all manipulations take precautions to minimize the loss of alcohol by evaporation.

Frothing—Liquids that froth to a troublesome extent during distillation may be strongly acidified with phosphoric or sulfuric acid, or treated with a slight excess of calcium chloride solution, or with a little paraffin or beeswax, before distillation.

Bumping—Bumping may be prevented during distillation by making the solution alkaline with milk of magnesia, or by adding porous chips of insoluble material, glass beads, or capillary tubes each sealed off at one end.

Glycerin—Dilute liquids that contain glycerin with sufficient water so that the residue, after distillation, contains at least 50 percent of water.

Iodine—Treat all solutions containing free iodine before distilling with powdered zinc or decolorize with just sufficient sodium thiosulfate solution (1 in 10), followed by a few drops of sodium hydroxide T.S.

Volatile Substances—Spirits, elixirs, tinctures, and similar preparations that contain appreciable proportions of volatile materials other than alcohol and water, such as volatile oils, chloroform, ether, camphor, etc., require special treatment, as follows:

For Liquids Presumed to Contain Less than 50 Percent of Alcohol—Mix 25 ml. of the sample, accurately measured, with about an equal amount of water in a separator. Saturate this mixture with sodium chloride, then add 25 ml. of solvent hexane, and shake the mixture to extract the interfering volatile ingredients. Draw off the separated, lower layer into a second separator, and repeat the extraction twice with two further 25-ml. portions of solvent hexane. Extract the combined solvent hexane solutions with three 10-ml. portions of a saturated solution of sodium chloride. Combine the saline solutions, and distil the mixture in the usual manner, collecting a volume of distillate having a simple ratio to the volume of the original sample.

For Liquids Presumed to Contain More than 50 Percent of Alcohol—Adjust the sample to a concentration of approximately 25 percent of alcohol by diluting it with water, then proceed as directed in the preceding paragraph, beginning with "Saturate this mixture with sodium chloride."

If volatile oils are present in small proportions only, and a cloudy distillate is obtained, the solvent hexane treatment not having been employed, the distillate may be clarified and rendered suitable for the specific gravity determination by shaking it with about one-fifth its volume of solvent hexane, or by filtering it through a thin layer of talc.

Other Preparations Requiring Special Treatment—Preparations containing free ammonia must be rendered slightly acid with sulfuric acid before being distilled. If volatile acids are present the preparation must be rendered slightly alkaline with sodium hydroxide.

Nitrite ester preparations must be treated with a small excess of sodium hydroxide before being distilled. The use of this expedient in examining nitrite ester preparations necessitates that a suitable correction be subtracted from the apparent result of the alcohol determination to compensate for the alcohol produced during the decomposition of the nitrite ester.

Preparations containing soap are treated with an excess of sulfuric acid to effect decomposition of the soap before they are extracted with solvent hexane as directed in the procedure for *Volatile Substances.*

Gas-Liquid Chromatographic Procedure

For liquids containing more than 10 percent alcohol, prepare two standard alcohol solutions, such that the concentrations are, respectively, about 5 percent less than and about 5 percent greater than the expected concentration of the sample, by diluting with water.

For liquids containing less than 10 percent alcohol, accurately prepare two standard alcohol solutions such that the concentrations are, respectively, about 1 percent less than and about 1 percent greater than the expected concentration, by diluting with water.

Treat the sample to be tested and each of the two standard alcohol solutions as follows: Transfer 10.0 ml. to a suitable glass-stoppered container, add 4.0 ml. of the internal standard (acetone, unless otherwise specified in the monograph), and mix. Add water only if necessary to effect solution. Inject an appropriate sample of the preparation into the chromatograph. Under typical conditions the instrument contains a 2-meter by 6-mm. ($^1/_4$-inch) outside diameter column packed with polyethylene glycol 400, 20 percent on calcined chromatographic silica; the column is maintained at a temperature of 100°; the injection port is equipped with a solids filter, and is maintained at 160°; and helium is used as the carrier gas at a flow rate of about 60 ml. per minute. From the chromatogram obtained as described above, or under other suitable conditions, calculate the ratio of the alcohol peak area to the internal standard peak area.

Calculate the percent of alcohol in the sample by the formula $[A(Y - Z) + B(Z - X)]/(Y - X)$, where A and B are the percent of alcohol in the lower and higher standards, respectively; X, Y, and Z are the ratios of the alcohol peak areas to the internal standard peak areas for the lower standard, higher standard, and the sample, respectively. If the value obtained is outside the range of values bracketed by the standards, repeat the procedure using standards that provide a range which includes the value of the sample.

ALKALOIDAL DRUG ASSAYS, PROXIMATE ASSAYS

Most alkaloids are practically insoluble in water, but soluble in certain organic solvents immiscible with water, such as chloroform, ether, amyl alcohol, benzene, etc., or mixtures of these. Salts of alkaloids, however, are usually soluble in water, but in most cases insoluble in nearly all of the organic solvents. The process of assay by immiscible solvents, generally known as the "shaking out" process, is based on these properties of alkaloids. It is carried out by treating the drug, or a concentrated liquid extract of it, with a solvent immiscible with water, in the presence of an excess of alkali which liberates the alkaloid. The free alkaloid is dissolved by the immiscible solvent from which it is removed by means of an excess of dilute acid. The acid solutions are then extracted with an immiscible solvent in the presence of an excess of alkali, and the immiscible solvent evaporated to obtain the alkaloid which is either weighed or determined volumetrically.

Preparation of the Drug for Assay—Grind the drug to be extracted to a powder of the fineness designated (see page 849). Care should be taken to avoid the loss of water during the powdering of the drug. If it is impossible to avoid this loss, dry the drug at a low temperature before powdering, note the loss of water, and make a correction in the final calculations.

Weighing for Assay—In weighing bulky, crude drugs for the assay an accuracy to within 10 mg. for quantities of 5 g. and over is sufficient. Portions of pilular extracts or ointments may be weighed on a piece of waxed or parchmentized paper, the surplus paper cut away, and the paper with the sample dropped into the vessel containing the solvent. In transferring weighed portions to a separator thoroughly rinse the vessel in which the material to be assayed was weighed and add the rinsings to the separator.

Extraction of Drugs—The alkaloidal content of alkaloid-bearing drugs is usually extracted by one of the following methods:

A. Maceration—Treat an accurately weighed portion of the ground drug with the specified solvent or mixture of solvents, made alkaline with ammonia T.S., and thoroughly mixed. Allow to macerate for 12 to 24 hours with occasional agitation or for a shorter period with continuous agitation. At the end of this period, allow the drug to settle, decant an aliquot of the solvent, and treat as described for the *Purification of the Alkaloids*.

B. Percolation—Place an accurately weighed quantity of the ground drug in a suitable container and saturate it with the specified solvent or mixture of solvents, and allow to stand for 5 minutes. Add a quantity of ammonia T.S. sufficient to make the mixture distinctly alkaline and mix thoroughly with the drug. Transfer the mixture to a cylindrical percolator, previously prepared by packing the outlet with purified cotton. Use a small amount of the solvent to rinse the container and add the rinsing to the percolator. Allow the drug to macerate for a suitable period of time (from 1 to 12 hours or overnight, depending upon the drug to be assayed). Then pack the drug firmly, place a pledget of purified cotton above it, and percolate slowly with the solvent until the drug is completely exhausted of its alkaloid content. Determine the completeness of extraction of the alkaloid by evaporating about 4 ml. of the last percolate to dryness, dissolving the residue in 0.5 ml. of approximately 0.5 *N* acid, and adding a drop of mercuric iodide T.S. (Valser's Reagent): not more than a slight turbidity is produced. Treat the percolate as directed for *Purification of the Alkaloids*.

C. Continuous Extraction—Place an accurately weighed portion of the ground drug in an extraction thimble and insert the thimble into a suitable extractor (a Soxhlet extractor of appropriate size is satisfactory). Moisten the drug with the specified solvent, mix by means of a stirring rod, and allow to stand about 5 minutes. Render the mixture alkaline with the specified quantity of ammonia T.S. and mix thoroughly. Rinse the stirring rod with a small portion of the solvent and allow the drug to macerate for 6 to 12 hours or overnight. Then pack the drug in the thimble, cover it with a pledget of purified cotton, add a sufficient quantity of solvent, and extract the drug for a specified period of time or until completely extracted.

Purification of the Alkaloids—The alkaloidal solution obtained by any of the extraction methods is usually contaminated with other extractives which interfere with the quantitative determinations of the alkaloids. To effect their purification remove the alkaloids from the immiscible solvent by shaking out with an acid, then render the acid solution alkaline, usually with an alkali hydroxide, and extract with an immiscible solvent.

The volume and strength of the acid to be used are usually left to the discretion of the operator. It is best, however, to keep the total volume as small as possible. For the first extraction, use at least 10 ml. of approximately 1 *N* acid or sufficient to render the mixture distinctly acid. When the drug contains a large amount of fat, use a smaller volume of more concentrated acid to prevent emulsions in the first extraction. For succeeding extractions, use a dilution of 5 ml. of the acid with 5 ml. of water. In all assays, continue the extraction until 0.5 ml. of the last acid washing shows not more than a slight turbidity on the addition of a drop of mercuric iodide T.S. (Valser's Reagent). The acid extracts, before proceeding with the next step, should be clear or practically so. If not clear, filter or treat as follows: Shake the combined acid extracts with one or more 10-ml. portions of the appropriate immiscible solvent until the acid solution is clear or practically so. Then wash the immiscible solvent extracts with one or more 5-ml. portions of water acidified with hydrochloric or sulfuric acid, and add these washings to the acid solution.

Then make the acid solution alkaline, in most cases with ammonia T.S., and extract it with several successive portions of the appropriate immiscible solvent. Use a volume of the latter in each operation not less than half that of the water solution, and repeat the operation as long as any alkaloid is extracted by the immiscible solvent. To determine the completeness of extraction, evaporate 1 ml. of the last extraction and dissolve the residue in 0.5 ml. of approximately 0.5 *N* hydrochloric acid: the resulting solution shows not more than a slight turbidity on the addition of a drop of mercuric iodide T.S. (Valser's Reagent). The number of extractions required depends largely on the character of the alkaloid. With most alkaloids extract several times before testing.

Washing—Wash carefully the stems of separators and funnels and the lips of flasks, separators, and graduates, from which solvents containing alkaloids, have been drawn or poured, with some of the solvent to prevent loss and to remove any of the alkaloids left by evaporation. Add these washings to the other extractions containing the alkaloids.

Determination of Alkaloids—Evaporate the solution of the purified alkaloids in the immiscible solvent to dryness on a steam bath or with a current of air. When the alkaloidal residue is to be determined volumetrically, soften it by the addition of about 1 ml. of neutralized alcohol or ether, add an accurately measured volume of standard acid, equivalent to about one and one-half to twice the volume estimated for the quantity of alkaloid present, and warm the mixture gently to ensure the complete solution of the alkaloid. If preferred, dissolve the alkaloidal residue in chloroform, add the standard acid, and remove the chloroform completely by evaporation. Then add a sufficient quantity of water to make the volume of the mixture measure at least 25 ml. and titrate the excess of acid with standard alkali, using 1 to 2 drops of the appropriate indicator.

If the alkaloidal residue is to be weighed, dry it to constant weight at 105°. If the final solvent has been chloroform, remove the last traces of that solvent by the addition of a few ml. of neutralized ether or alcohol, followed by evaporation. Avoid loss by decrepitation, especially when evaporating chloroform solutions of nux vomica alkaloids, by the addition of a little alcohol after the solution has been reduced to a volume of 1 or 2 ml., and evaporate at a low temperature, rotating the container during the evaporation.

Indicators—Unless otherwise directed in the individual monograph, use methyl red T.S. as the indicator in volumetric determinations and for standardizing volumetric solutions.

Aliquots—When using aliquots, measure the solvent and the aliquot at the same temperature. When handling volatile liquids, a lower temperature and a more quickly conducted operation reduce the loss by evaporation.

Apparatus for Proximate Assays—When a container of definite size and shape is recommended in a proximate assay process, it is advisory, but when volumetric flasks, measuring burets, or other exact measuring apparatus are specified their use is obligatory.

Adsorbents—In assaying fluidextracts, tinctures, and other preparations of alkaloid-bearing drugs, it is often necessary to evaporate these to dryness and, to avoid loss and to aid in the evaporation, they are usually added to some adsorbent material. For this purpose use paper pulp or asbestos fibers previously acid- and alkali-washed and then rendered neutral by washing with water and dried before use.

Emulsions—Shake or rotate a water solution with an immiscible solvent in a separator for about 1 minute. Avoid long or violent agitation as emulsions are likely to form, especially in alkaline solutions. Belladonna leaves sometimes contain saponins which cause troublesome emulsions. If emulsions prove persistent, draw off the emulsified portion, and add an excess of either solvent. This usually breaks the emulsion and permits a complete separation. A separated emulsion may sometimes be broken by the addition of a small amount of anhydrous sodium sulfate. If this is done, wash the residue with additional solvent to remove the alkaloid completely.

Emulsification may sometimes be prevented by increasing the volume of the water or of the immiscible solvent. Chloroform and ether solutions of drugs which contain large proportions of fat may form troublesome emulsions. In such cases, add sufficient sulfuric acid to acidify and evaporate the volatile solvent, while stirring with a glass rod. When the resinous and fatty matter has been agglutinated, cool the acid solution and filter it through a small, wetted filter into a separator. Redissolve the residue in 15 ml. of ether, add 5 to 10 ml. of 0.1 *N* acid, evaporate the ether as before, with continued stirring, and pour the acid solution through the filter into the separator. Repeat the extraction of the fatty residue with dilute acid 2 or 3 times and finally wash the filter free from alkaloids.

AMPHETAMINE ASSAY

Standard Preparation—Dissolve a suitable quantity of USP Dextroamphetamine Sulfate Reference Standard, previously dried at 105° for 2 hours and accurately weighed, in chloroform-saturated sulfuric acid solution (1 in 20), and dilute quantitatively to prepare a solution containing about 500 mcg. of dextroamphetamine sulfate in each ml.

Assay Preparation—Prepare as directed in the individual monograph.

Preparation of the Chromatographic Column—Pack a pledget of fine glass wool in the base of a chromatographic tube with the aid of a tamping rod about 40 cm. long and having a terminal disk with a diameter about 1 mm. less than that of the tube. (A suitable chromatographic tube consists of a 25 × 300-mm. test tube to which is fused a 5-cm. length of 7-mm. glass tubing.) Place 2 g. of purified siliceous earth in a 100-ml. beaker, add 1 ml. of hydrochloric acid solution (1 in 100), and mix until a fluffy mixture is obtained. Transfer the mixture to the column, and tamp moderately to compress the material into a uniform mass. Transfer the *Assay preparation* to the column, dry-rinse the beaker with 1 g. of purified siliceous earth, and transfer to the column. Tamp a pledget of fine glass wool into place at the top of the column.

Procedure—Wash the column with 100 ml. of water-saturated chloroform, and discard the washings. Place under the column, as a receiver, a 125-ml. separator containing 10.0 ml. of chloroform-saturated sulfuric acid solution (1 in 20). Pass through the column 35 ml. of ammoniacal chloroform, prepared by equilibrating 2 ml. of stronger ammonia water and 100 ml. of chloroform, and complete the elution with 70 ml. of water-saturated chloroform. Remove the separator, shake it vigorously for 1 minute, allow the layers to separate, discard the chloroform layer, and use the 10.0-ml. acid solution of the sulfate salt of the amphetamine as the *Sample Solution*. Concomitantly determine the absorbance of the *Sample Solution* and the *Standard Preparation* at 280 mμ and at the maximum at about 257 mμ, in 1-cm. cells, with a suitable spectrophotometer, using chloroform-saturated sulfuric acid solution (1 in 20) as the blank. Designate the absorbance from the *Sample Solution* as A_U, and that from the *Standard Preparation* as A_S, and make the calculation as directed in the individual monograph.

ANTIBIOTICS

The term "antibiotic" is used in this National Formulary to designate a medicinal preparation containing a significant quantity of a chemical substance that is produced by a microorganism or, although capable of being produced by a microorganism, is produced by chemical synthesis and that in dilute solution has the capacity to inhibit or destroy microorganisms. Under the terms of the Federal Food, Drug, and Cosmetic Act of 1938, as amended by Public Law 87-781 ("Drug Amendments of 1962"), all antibiotics intended for use in man are subject to production and testing controls under federal regulation, including batch certification prior to distribution. For the purposes of administering the certification program, standards of potency and purity for antibiotics are established by the Food and Drug Administration in the form of regulations published from time to time in the Federal Register.

Since all of the antibiotics recognized in this National Formulary are subject to the provisions of the regulations, the latter determine the compendial standards. Therefore, the NF monographs on antibiotics include only those aspects of identity, purity, potency, and packaging and storage that are of special interest to medical and pharmaceutical practitioners. As is indicated in the Notice on page ii, any revisions of the federal requirements affecting substantially the NF monographs will be made the subject of NF Supplements as promptly as practicable.

Labeling—Antibiotics intended for parenteral use comply with the requirements for *Labeling* under *Injections,* page 810. In addition, the labeling carries information required by the federal regulations, including an expiration date, which may differ among distributors for any given product according to specific exemptions allowed by the Food and Drug Administration.

ARSENIC TEST

Silver Diethyldithiocarbamate Colorimetric Method

Reagents used in this test, other than the arsenic trioxide, should have as low a content of arsenic as possible.

Apparatus—The apparatus (see illustration)* consists of an arsine generator (*a*) fitted with a scrubber unit (*c*) and an absorber tube (*e*), with standard-taper or ground glass ball-and-socket joints (*b* and *d*) between the units. Alternatively, an apparatus embodying the principle of the assembly described and illustrated may be used. (Addition of a small amount of isopropyl alcohol to the generator can improve the uniformity of the rate of gas evolution.)

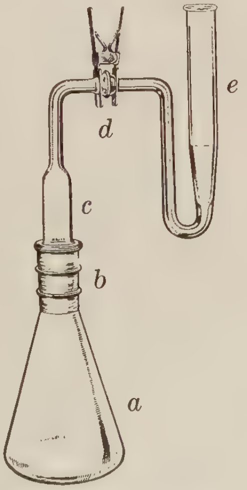
Standard Arsenic Solution—Dissolve 132.0 mg. of arsenic trioxide that has been finely pulverized, dried over sulfuric acid and accurately weighed, in 5 ml. of sodium hydroxide solution (1 in 5) in a 1000-ml. volumetric flask. Neutralize the solution with diluted sulfuric acid, add 10 ml. more of diluted sulfuric acid, then add recently boiled water to volume, and mix. Transfer 10.0 ml. of this solution into a 1000-ml. volumetric flask, add 10 ml. of diluted sulfuric acid, then add recently boiled water to volume, and mix. Each ml. of *Standard Arsenic Solution* contains the equivalent of 1 mcg. of arsenic (As). Keep this solution in an all-glass container, and use within 3 days.

Test Preparation—*Caution: Some substances may react unexpectedly with explosive violence when digested with hydrogen peroxide. Employ appropriate safety precautions at all times.*

NOTE: If halogen-containing compounds are present, use a lower temperature while heating the sample with sulfuric acid, do not boil the mixture, and add the hydrogen peroxide, with caution before charring begins, to prevent loss of trivalent arsenic.

Test preparations of inorganic compounds are prepared as directed in the individual monograph.

Test preparations of organic compounds are prepared in the generator flask (*a*), unless otherwise directed in the individual monograph, according to the following general procedure: Transfer the quantity



Arsenic Test Apparatus

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* A suitable apparatus is obtainable from Fisher Scientific Co., 1717 Forbes St., Pittsburgh, PA 15219 (Catalog No. 1-405).

of the test substance specified in the monograph to the generator flask, add 5 ml. of sulfuric acid and a few glass beads, and digest on a hot plate or other suitable heating unit in a fume hood until charring begins. (Additional sulfuric acid may be necessary to completely wet some samples, but the total volume added should not exceed 10 ml.) After the sample has been initially decomposed by the acid, cautiously add, dropwise, 30 percent hydrogen peroxide, allowing the reaction to subside and reheating between drops. The first few drops must be added very slowly with sufficient mixing to prevent a rapid reaction, and discontinue heating if foaming becomes excessive. When the reaction has abated, heat cautiously, rotating the flask occasionally to prevent the sample from caking on glass exposed to the heating unit. *Maintain oxidizing conditions at all times during the digestion by adding small quantities of the hydrogen peroxide solution whenever the mixture turns brown or darkens.* Continue the digestion until the organic matter is destroyed, fumes of sulfur trioxide are copiously evolved, and the solution becomes colorless or retains only a light straw color. Cool, add cautiously 10 ml. of water, mix well, and again evaporate to strong fuming, repeating this procedure, if necessary, to remove any trace of hydrogen peroxide. Cool, add cautiously 10 ml. of water, wash the sides of the flask with a few ml. of water, and dilute to 35 ml. with water.

Procedure—If the *Test Preparation* was not prepared in the generator flask (*a*), transfer a volume of the solution prepared as directed in the individual monograph, to the flask, and add water to make 35 ml. Add 20 ml. of dilute sulfuric acid (1 in 5), 2 ml. of potassium iodide T.S., and 0.5 ml. of stronger acid stannous chloride T.S., and mix. Allow to stand for 30 minutes at room temperature. Pack the scrubber tube (*c*) with two pledgets of cotton that have been soaked in saturated lead acetate solution, freed of excess solution by expression, and dried in a vacuum at room temperature, leaving a small space between the two pledgets. Lubricate the joints (*b* and *d*) with a suitable stopcock grease (designed for use with organic solvents), and connect the scrubber unit with the absorber tube (*e*). Transfer 3.0 ml. of silver diethyldithiocarbamate T.S. to the absorber tube. Alternatively, a larger accurately measured volume of the silver diethyldithiocarbamate T.S. may be employed, provided that the same volume is used for the control test and that the apparatus will accommodate the larger volume. Add 3.0 g. of granular zinc (No. 20 mesh) to the mixture in the flask, immediately insert the standard-taper joint of the assembled scrubber unit, place the generator flask (*a*) in a water bath at 25 ± 3°, and allow the evolution of hydrogen and the color development to proceed for 45 minutes, swirling the flask gently at 10-minute intervals. Disconnect the absorber tube from the generator and scrubber units, and transfer the absorbing solution to a 1-cm. absorption cell. Determine the absorbance at 525 mμ with a suitable spectrophotometer or colorimeter, using silver diethyldithiocarbamate T.S. as the blank. The absorbance due to any red color from the solution of the sample does not exceed that produced by 10.0 ml. of *Standard Arsenic Solution* (10 mcg. As) when treated with the same quantities of the same reagents and in the same manner. If the *Test Preparation* was prepared as directed in the general procedure for organic compounds, mix the portion of *Standard Arsenic Solution* with 2 ml. of sulfuric acid and the total amount of 30 percent hydrogen peroxide used in the oxidation of the sample, and heat the mixture to strong fuming. Cool, add cautiously 10 ml. of water, again evaporate to strong fuming, and cool. Dilute with water to 35 ml., and proceed as directed under *Procedure*, beginning with "Add 20 ml. of dilute sulfuric acid (1 in 5). . . ."

BACTERIOSTATIC AGENTS

Assay for Benzyl Alcohol

Internal Standard Solution—Transfer 2.0 ml. of liquified phenol to a 50-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 5.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with water, and mix.

Standard Preparation—Transfer about 900 mg. of benzyl alcohol, accurately weighed, to a 100-ml. volumetric flask, add methanol to volume, and mix. Transfer 2.0 ml. of this solution to a 10-ml. volumetric flask, dilute to volume with *Internal Standard Solution*, and mix.

Test Preparation—Transfer 2.0 ml. of the sample solution to a 10-ml. volumetric flask, dilute to volume with *Internal Standard Solution*, and mix.

Procedure—Inject 5 μl. of the *Standard Preparation* into a suitable gas chromatograph (see page 787) equipped with a flame-ionization detector, and record the chromatogram. Under typical conditions, the instrument contains a 1.8-m. × 6-mm. (outside diameter) column packed with 5 percent polyethylene glycol 20,000 on flux-calcined acid-washed silanized chromatographic siliceous earth* or other suitable support. The column is maintained at 140°, the injection port at 310°, and the detector block at 275°. Helium or nitrogen is used as the carrier gas at a flow rate of about 50 ml. per minute. Measure the areas under the benzyl alcohol and the phenol peaks, recording the values as P_1 and P_2, respectively. Calculate the standard ratio, R_S, by the formula P_1/P_2.

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* A suitable grade is "Diatoport S", available from Hewlett-Packard, F & M Scientific Division, Avondale, PA 19311.

Inject 5 µl. of the *Test Preparation* into the chromatograph, and record the chromatogram under the same conditions. Record the area under the benzyl alcohol peak as p_1 and that under the phenol peak as p_2. Calculate the sample ratio, R_U, by the formula p_1/p_2.

Calculate the quantity, in mg., of benzyl alcohol (C_7H_8O) in each ml. of the sample taken by the formula $5C \times (R_U/R_S)$, in which C is the exact concentration, in mg. per ml., of the *Standard Preparation.*

Assay for Chlorobutanol

Internal Standard Solution—Transfer 0.6 ml. of benzaldehyde to a 500-ml. volumetric flask, add 25 ml. of methanol, dilute to volume with water, and mix.

Standard Preparation—Transfer about 500 mg. of anhydrous chlorobutanol, accurately weighed, to a 100-ml. volumetric flask, dissolve in 5 ml. of methanol, dilute to volume with water, and mix. Transfer 1.0 ml. of this solution to a 25-ml. volumetric flask, add 1.0 ml. of *Internal Standard Solution,* dilute to volume with 5 percent methanol, and mix.

Test Preparation—Transfer 1.0 ml. of the sample solution to a 25 ml. volumetric flask, add 1.0 ml. of *Internal Standard Solution,* dilute to volume with 5 percent methanol, and mix.

Procedure—Inject 5 µl. of the *Standard Preparation* into a suitable gas chromatograph (see page 787) equipped with a flame-ionization detector, and record the chromatogram. Under typical conditions, the instrument contains a 1.2-m. × 6-mm. (outside diameter) column packed with 5 percent polyethylene glycol 20,000 on flux-calcined acid-base washed silanized chromatographic siliceous earth† or other suitable support. The column is maintained at 110°, and the injection port and the detector block at 270°. Helium or nitrogen is used as the carrier gas at a flow rate of about 40 ml. per minute. Measure the areas under the chlorobutanol and the benzaldehyde peaks, recording the values as P_1 and P_2, respectively. Calculate the standard ratio, R_S, by the formula P_1/P_2.

Inject 5 µl. of the *Test Preparation* into the chromatograph, and record the chromatogram under the same conditions. Record the area under the chlorobutanol peak as p_1 and that under the benzaldehyde peak as p_2. Calculate the sample ratio, R_U, by the formula p_1/p_2.

Calculate the quantity, in mg., of chlorobutanol ($C_4H_7Cl_3O$) in each ml. of the sample taken by the formula $0.025C \times R_U/R_S$, in which C is the exact concentration, in mcg. per ml., of the *Standard Preparation.*

Assay for Methylparaben and Propylparaben

Internal Standard Solution—Transfer 80 mg. of 2-naphthol to a 100-ml. volumetric flask, add ether to volume, and mix.

Standard Preparation A—Transfer about 100 mg. of methylparaben and about 10 mg. of propylparaben, accurately weighed, to a 200-ml. volumetric flask, add *Internal Standard Solution* to volume, and mix.

Standard Preparation B—Transfer 10.0 ml. of *Standard Preparation A* to a 25-ml. conical flask, and continue as directed under *Test Preparation,* beginning with "Add 3 ml. of pyridine. . . ."

Test Preparation—Transfer 10.0 ml. of the sample solution to a separator, add 10.0 ml. of *Internal Standard Solution,* shake vigorously, and filter the ether layer through anhydrous sodium sulfate into a suitable container. Extract the aqueous phase with two 10-ml. portions of ether, filtering each extract through the anhydrous sodium sulfate. Evaporate the combined extracts under a stream of dry air until the volume is reduced to about 10 ml., and then transfer quantitatively to a 25-ml. conical flask. Add 3 ml. of pyridine, complete the evaporation of the ether, and then boil on a hot plate until the volume is reduced to about 1 ml. Cool, and add 1.0 ml. of a suitable silylation agent, such as hexamethyldisilazane plus trimethylchlorosilane, bis(trimethylsilyl)acetamide, or bis(trimethylsilyl)trifluoroacetamide. Mix, and allow to stand for at least 15 minutes.

Procedure—Inject 2 µl. of *Standard Preparation B* into a suitable gas chromatograph (see page 787) equipped with a flame ionization detector. Under typical conditions, the instrument contains a 1.8-m. × 3-mm. (outside diameter) column packed with 5 percent methyl silicone gum rubber** on flux-calcined acid washed silanized chromatographic siliceous earth* or other suitable inert support. The column is maintained at 150°, and the injection port and detector block at 200°. Helium or nitrogen is used as the carrier gas at a flow rate of about 20 ml. per minute. Measure the areas under the methylparaben, propylparaben, and 2-naphthol peaks, recording the values as P_1, P_2, and P_3, respectively. Calculate the standard methylparaben ratio, R_M, by the formula P_1/P_3, and calculate the standard propylparaben ratio, R_P, by the formula P_2/P_3.

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† A suitable grade is "Anakrom ABS", available from Analabs, Inc., Hamden, CT 06518.

** A suitable grade is "GC Grade Silicone SE-30," available from the General Electric Corp., Schenectady, NY 12305.

Inject 2 µl. of the *Test Preparation* into the chromatograph, and record the chromatogram under the same conditions. Record the areas under the methylparaben, propylparaben, and 2-naphthol peaks as p_1, p_2, and p_3, respectively. Calculate the sample methylparaben ratio, r_m, by the formula p_1/p_3, and calculate the sample propylparaben ratio, r_p, as p_2/p_3.

Calculate the quantity, in mcg., of methylparaben ($C_8H_8O_3$) in each ml. of the sample taken by the formula $C \times (r_m/R_M)$, in which C is the exact concentration, in mcg. per ml., of methylparaben in *Standard Preparation A*.

Calculate the quantity, in mcg., of propylparaben ($C_{10}H_{12}O_3$) in each ml. of the sample taken by the formula $C \times (r_p/R_P)$, in which C is the exact concentration, in mcg. per ml., of propylparaben in *Standard Preparation A*.

Assay for Phenol

Internal Standard Solution—Transfer 1.0 ml. of benzyl alcohol to a 100-ml. volumetric flask, dilute to volume with methanol, and mix. Transfer 10.0 ml. of this solution to a 50-ml. volumetric flask, dilute to volume with methanol, and mix.

Standard Preparation—Transfer about 250 mg. of phenol, accurately weighed, to a 100-ml. volumetric flask, add 25 ml. of methanol, dilute to volume with water, and mix. Transfer 3.0 ml. of this solution to a 10-ml. volumetric flask, add 2.0 ml. of *Internal Standard Solution*, dilute to volume with water, and mix.

Test Preparation—Transfer 3.0 ml. of the sample solution to a 10-ml. volumetric flask, add 2.0 ml. *Internal Standard Solution*, dilute to volume with water, and mix.

Procedure—Inject 3 µl. of the *Standard Preparation* into a suitable gas chromatograph (see page 787) equipped with a flame-ionization detector, and record the chromatogram. Under typical conditions, the instrument contains a 1.2-m. × 6-mm. (outside diameter) column packed with 5 percent polyethylene glycol 20,000 on flux-calcined acid-base washed silanized chromatographic siliceous earth† or other suitable support. The column is maintained at 145°, the injection port at 310°, and the detector block at 275°. Helium or nitrogen is used as the carrier gas at a flow rate of about 50 ml. per minute. Measure the areas under the phenol and the benzyl alcohol peaks, recording the values as P_1 and P_2, respectively. Calculate the standard ratio, R_S, by the formula P_1/P_2.

Inject 3 µl. of the *Test Preparation* into the chromatograph, and record the chromatogram under the same conditions. Record the area under the phenol peak as p_1 and that under the benzyl alcohol peak as p_2. Calculate the sample ratio, R_U, by the formula p_1/p_2.

Calculate the quantity, in mg., of phenol (C_6H_6O) in each ml. of the sample taken by the formula $3.33C \times R_U/R_S$, in which C is the exact concentration, in mg. per ml., of the *Standard Preparation*.

Assay for Phenylmercuric Nitrate

Standard Preparation—Transfer about 100 mg. of phenylmercuric nitrate, accurately weighed, to a 1000-ml. volumetric flask, dissolve in 0.1 *N* sodium hydroxide, warming if necessary to effect solution, dilute to volume with 0.1 *N* sodium hydroxide, and mix. Transfer 10.0 ml. of this solution to a 25-ml. volumetric flask, and continue as directed under *Test Preparation*, beginning with "...add 2 ml. of 0.1 *N* potassium nitrate...."

Test Preparation—Transfer 10.0 ml. of the sample solution to a 25-ml. volumetric flask, add 2 ml. of 0.1 *N* potassium nitrate and 10 ml. of pH 9.2 alkaline borate buffer solution (see page 783), and adjust the pH to 9.2, if necessary, by the addition of diluted nitric acid. Add 1.5 ml. of freshly prepared gelatin solution (1 in 1000), dilute to volume with the pH 9.2 alkaline borate buffer solution, and mix.

Procedure—Transfer a portion of the *Test Preparation* to a polarographic cell, and deaerate by bubbling nitrogen through the solution for 15 minutes. Insert the dropping mercury electrode of a suitable polarograph (see page 847), and record the polarogram from −0.6 to −1.5 volts. Determine the height of the diffusion current $[(i_d)_U]$ as the difference between the residual current and the diffusion current plateau, versus the saturated calomel electrode. Concomitantly and similarly determine the diffusion current $[(i_d)_S]$ of the *Standard Preparation*. Calculate the quantity, in mcg., of phenylmercuric nitrate ($C_6H_5HgNO_3$) in each ml. of the sample taken by the formula $2.5C \times [(i_d)_U/(i_d)_S]$, in which C is the exact concentration, in mcg. per ml., of the *Standard Preparation*.

Assay for Thimerosal

Standard Preparation—On the day of use, transfer about 100 mg. of NF Thimerosal Reference Standard, accurately weighed, to a 1000-ml. volumetric flask, add water to volume, and mix. Protect from light. Transfer 15.0 ml. of this solution to a 25-ml. volumetric flask, add 1.5 ml. of gelatin solution (1 in 1000), dilute to volume with 0.1 *N* potassium nitrate, and mix.

Test Preparation—Transfer 15.0 ml. of the sample solution to a 25-ml. volumetric flask, add 1.5 ml. of gelatin solution (1 in 1000), dilute to volume with 0.1 *N* potassium nitrate, and mix.

Procedure—Transfer a portion of the *Test Preparation* to a polarographic cell, and deaerate by bubbling nitrogen through the solution for 15 minutes. Insert the dropping mercury electrode of a suitable polarograph (see page 847), and record the polarogram from -0.2 to -1.4 volts. Determine the height of the diffusion current $[(i_d)_U]$ as the difference between the residual current and the diffusion current plateau, versus the saturated calomel electrode. Concomitantly and similarly determine the diffusion current $[(i_d)_S]$ of the *Standard Preparation*. Calculate the quantity, in mcg., of thimerosal ($C_9H_9HgNaO_2S$) in each ml. of the sample taken by the formula $1.667C \times [(i_d)_U/(i_d)_S]$, in which C is the exact concentration, in mcg. per ml., of the *Standard Preparation*.

BARBITURATE ASSAY

Weigh accurately a portion of the powder, obtained as directed in the monograph, equivalent to about 300 mg. of the barbiturate, transfer it quantitatively to a separator, and dissolve it as completely as possible in 10 ml. of alkaline sodium chloride T.S. Extract the mixture with two 15-ml. portions of ether, and discard the ether. Add 2 ml. of hydrochloric acid and 5 ml. of water, and mix. Completely extract the liberated acid barbiturate with chloroform. Test for completeness of extraction by extracting with an additional 10-ml. portion of chloroform and evaporating the solvent: not more than 500 mcg. of residue remains. Wash the combined chloroform extracts with 10 ml. of water acidified with a drop of hydrochloric acid, then extract the water with 10 ml. of chloroform, adding the latter to the main chloroform solution. Filter the chloroform solution through a pledget of cotton or other suitable filter, previously washed with chloroform, into a tared beaker, and finally wash the separator and filter with three 5-ml. portions of chloroform. Evaporate the combined chloroform solution and washings to dryness with the aid of a current of air on a steam bath, cool, add 10 ml. of ether, re-evaporate, dry the residue at 105° for 2 hours, cool, and weigh.

When Stearic Acid or Stearates are Present—Dissolve the weighed residue obtained as described in the preceding paragraph, or as modified in the individual monograph, in 10 ml. of alcohol, add 20 ml. of barium hydroxide T.S., and mix. Filter into a separator, wash the residue and the filter with three 10-ml. portions of barium hydroxide T.S., acidify the combined filtrate and washings with diluted hydrochloric acid, and extract completely with chloroform as before. Wash the combined chloroform extracts with 5 ml. of water acidified with a drop of hydrochloric acid, filter through a pledget of cotton or other suitable filter, previously washed with chloroform, into a tared beaker, and finally wash the separator and filter with three 5-ml. portions of chloroform. Evaporate the combined chloroform solution and washings to dryness with the aid of a current of air on a steam bath, cool, add 10 ml. of ether, re-evaporate, dry the residue at 105° for 2 hours, cool, and weigh.

BIOLOGICS

The antitoxins, antivenins, blood derivatives, immune serums, immunologic diagnostic aids, toxoids, vaccines, and related articles that are produced under license in accordance with the terms of the federal Public Health Service Act of 1944, as amended—as well as such products for which minimum requirements have been established by the Division of Biologics Standards of the National Institutes of Health—have long been known as "biologics." However, in Title III, Part F, of the Act, the term "biological products" is applied to the group of licensed products as a whole. For National Formulary purposes, the term "biologics" refers to those products that must be licensed under the Act and comply with Public Health Service Regulations—Part 73, pertaining to federal control of these products, as administered by the Division of Biologics Standards of the National Institutes of Health.

The nature of biologics is such as to necessitate a form of control beyond that which can be provided generally in the National Formulary. However, the National Formulary standards conform to the Public Health Service Regulations in covering those aspects of identity, purity, potency, and packaging and storage that are of particular interest to pharmacists and physicians responsible for the purchase, storage, and use of biologics. As is indicated in the Notice on page ii, revisions of the federal requirements affecting the NF monographs will be made the subjects of NF supplements as promptly as practicable.

Vehicles and Added Substances—Vehicles and added substances suitable for biologics are those named in the Public Health Service Regulations.

The choice of antibacterial agents for use in biologics requires special care and a demonstration of effectiveness with respect to both suppression of microbial growth and relative freedom from inactivation of the therapeutic principle.

Containers for Injections—Containers for biologics intended to be administered by injection meet the requirements for *Containers for Injections* under *Injections*, page 810.

Volume in Container—The volumes in containers of biologics intended to be administered by injection meet the requirements for *Volume in Container* under *Injections*, page 810.

Labeling—Biologics comply with the requirements for *Labeling* under *Injections*, page 810. In addition, the labeling for each biologic shows the NIH title (the name under which the product is licensed under the Public Health Service Act); the expiration date; the recommended storage temperature; the manufacturer's name, license number, and address; and such other information as the Public Health Service Regulations may require.

Packaging and Storage—As a class, biologics require unusual attention with respect to storage. The labeling gives the recommended storage temperature, which generally conforms to that maintained by the ordinary, household-type refrigerator. (Smallpox Vaccine and Yellow Fever Vaccine represent exceptions, since they are preserved at a temperature preferably below 0°, as in a refrigerator for frozen food.) The only precaution necessary in storing biologics in such refrigerators is that care be taken to avoid freezing. The risk of damage from freezing may be greatest with respect to the aqueous diluents frequently packaged with the biologics. Only in exceptional cases is the biologic itself harmed by freezing, provided that, in thawing, the container (including its closure) remains intact.

The nature of biologics is such that bacterial contamination or deterioration may result from subdividing the original package. For this reason, the biologics are to be dispensed in the unopened containers in which they were placed by the manufacturer.

BOILING OR DISTILLING RANGE OR TEMPERATURE

To determine the temperatures between which an official liquid boils or the percentage of the material that distils between two specified temperatures, use *Method I* or *Method II* as directed herein. The lower of the two temperatures is the thermometer reading when the first 5 drops of distillate have been collected, and the upper temperature is the reading when the last liquid evaporates from the bottom of the flask (Dry Point) or when the proportion specified in the individual monograph has been collected.

Method I—Use this method for liquids for which the permissible range in boiling temperature is 5° or less, unless otherwise specified in the individual monograph. In order to have the entire volatile portion distil over at the prescribed rate, it is best to make a preliminary distillation of a separate portion of 25 ml. of the liquid, during which the source of heat is regulated until the distillation proceeds at the prescribed rate. Stop the distillation, clean the flask, recharge it with a fresh portion of 25 ml. of the liquid, and conduct a new distillation as directed.

Apparatus—Use a distilling flask having a bulb of 50 to 60-ml. capacity and a neck 10 to 12 cm. long and 14 to 16 mm. in internal diameter. Attached about midway on the neck is an outlet tube 10 to 12 cm. long and 4 to 5 mm. in internal diameter, which forms an angle of 70° to 75° with the lower portion of the neck.

Use a straight glass condenser with a water jacket 40 to 60 cm. long, the distance from the upper end of the jacket to the neck of the flask being 18 to 25 cm.

Provide an asbestos board 12 to 15 cm. square and 3 to 5 mm. thick and having a circular perforation, located centrally, to hold the flask. The edge of the perforation should fit the flask closely when the latter is set into it. The size of the perforation should be such that when the flask is set into it the portion of the flask below the upper surface of the asbestos has a capacity of 3 to 4 ml.

In order to avoid the necessity for an emergent stem correction, an accurately standardized thermometer of the Anschütz type may be employed. When placed in position, the top of the bulb of the thermometer is level with the center of the opening of the outlet tube.

When a thermometer of Type VI or VII is employed, correct for the temperature of the emergent stem by the formula $0.00015 \times N(T - t)$, in which N represents the number of degrees of emergent stem from the bottom of the stopper, T, the observed temperatures of distillation, and t, the temperature registered by an auxiliary thermometer the bulb of which is placed midway of the emergent stem, adding the correction to the observed readings of the main thermometer.

Procedure—Place the asbestos board on a tripod or other suitable support. Place in the distilling flask 25 ml. of the liquid to be tested, insert the thermometer, stand the flask in an upright position in the perforation of the asbestos board, and connect it with the condenser. Then distil the liquid by the application of heat, from a suitable source, at the rate of 4 to 5 ml. per minute, noting the temperature as soon as 5 drops of the liquid have distilled into the receiver, and when the last liquid evaporates from the bottom of the flask or when the specified percentage has distilled over. Correct the observed temperature readings for any variation in the barometric pressure from the normal (760 mm.) by allowing 0.1 degree for each 2.7 mm. of variation, adding if the pressure is lower, or subtracting if higher than 760 mm., and apply the emergent stem correction when necessary.

Method II—Use this method with liquids for which the permissible range in boiling temperature exceeds 5°.

Apparatus—Use apparatus similar to that specified for *Method I*, except that the bulb of the distilling flask is of 200-ml. capacity, and the internal diameter of the neck is 18 to 24 mm. and that of the outlet tube is 5 to 6 mm. The perforation in the asbestos board is 50 mm. in diameter.

For liquids that distil below 80°, connect the condenser and the receiver by means of a suitable adapter fitted loosely enough to allow air to escape readily from the receiver. Arrange to keep the receiver immersed in ice to within 2.5 cm. of its top during the distillation.

Procedure—Place the distilling flask in an upright position in the perforation in the asbestos board, and connect it with the condenser. The outlet tube is to extend 25 to 35 mm. into the condenser beyond the connecting stopper.

Measure 100 ml. of the liquid to be tested, using a cylinder having 1-ml. graduations. Note the temperature of the liquid, and transfer it as completely as possible to the distilling flask. Use this cylinder as the receiver for the distillate without rinsing out any of the adhering liquid. Insert the thermometer, as described in *Method I*, and distil by the application of heat, at the rate of from 4 to 5 ml. per minute, collecting the distillate coming over between the temperatures specified in the individual monograph. Bring the distillate to the same temperature as that at which the liquid was originally measured, and note its volume. Correct the temperature reading for barometric pressure, and if necessary, for the emergent stem of the thermometer.

Cool all liquids that distil below 80° to between 10° and 15° before measuring the 100 ml. for the test.

BUFFERS

General Concepts—A solution is said to be buffered if it resists changes in the activity of an ion on the addition of substances which are expected to change the activity of that ion. Buffers are substances or combinations of substances which impart this resistance to a solution. Buffered solutions are systems in which the ion is in equilibrium with substances capable of removing or releasing the ion.

Buffer capacity refers to the amount of material which may be added to a solution without causing a significant change in ion activity. While this idea is qualitatively accepted, there is no generally accepted quantitative definition of this solution parameter. The capacity of a buffered solution must be adjusted to the conditions of use, usually by adjustment of the concentrations of buffer substances.

Buffers are used to establish and maintain an ion activity within narrow limits. The most common systems are used (a) to establish hydrogen ion activity for the calibration of pH meters, (b) in the preparation of dosage forms which approach isotonicity, (c) in various analytical procedures, and (d) to maintain stability of various dosage forms. Buffers used in physiological systems must be carefully chosen so as not to interfere with pharmacological activity of the medicament or normal function of the organism. Buffers used in chemical analysis must be compatible with the substance determined and the reagents used.

Standard Buffer Solutions—Standard solutions of definite pH are readily available in buffer solutions prepared from the appropriate reagents. In addition, buffer solutions, buffer tablets, and buffer solids may be obtained from commercial sources in convenient pre-packaged form. These cover the working range in pharmaceutical practice but are not recommended for pH meter standardization (see page 824).

The required reagents are described in the section, *Reagents, Indicators and Solutions*, USP XVIII. Previously dry the crystalline reagents, except the boric acid, at 110° to 120° for 1 hour. Store the prepared solutions in chemically resistant, tight containers such as Type I glass bottles. Use the solutions within 3 months.

Standard Buffer Solutions for various ranges between pH 1.1 and pH 10.0 may be prepared by appropriate combinations of 0.2 *M* solutions described herein, used in the proportions shown in the table. The volumes shown in the table are for 200 ml. of buffer solution.

1. *Hydrochloric Acid, 0.2 M, and Sodium Hydroxide, 0.2 M*—Prepare and standardize as directed under *Volumetric Solutions*, USP XVIII.

2. *Potassium Biphthalate, 0.2 M*—Dissolve 40.846 g. of potassium biphthalate ($KHC_6H_4[COO]_2$) in water, and dilute to 1000 ml.

3. *Potassium Phosphate, Monobasic, 0.2 M*—Dissolve 27.218 g. of monobasic potassium phosphate (KH_2PO_4) in water, and dilute to 1000 ml.

4. *Boric Acid and Potassium Chloride, 0.2 M*—Dissolve 12.369 g. of boric acid (H_3BO_3) and 14.911 g. of potassium chloride (KCl) in water, and dilute to 1000 ml.

5. *Potassium Chloride, 0.2 M*—Dissolve 14.911 g. of potassium chloride (KCl) in water, and dilute to 1000 ml.

Composition of Standard Buffer Solutions

Hydrochloric Acid Buffer

Place 50 ml. of the potassium chloride solution in a 200-ml. volumetric flask, add the specified volume of the hydrochloric acid solution, then add water to volume.

pH	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2
HCl, ml.	85.0	67.2	53.2	41.4	32.4	26.0	20.4	16.2	13.0	10.2	7.8

Acid Phthalate Buffer

Place 50 ml. of the potassium biphthalate solution in a 200-ml. volumetric flask, add the specified volume of the hydrochloric acid solution, then add water to volume.

pH	2.2	2.4	2.6	2.8	3.0	3.2	3.4	3.6	3.8	4.0
HCl, ml.	49.5	42.2	35.4	28.9	22.3	15.7	10.4	6.3	2.9	0.1

Neutralized Phthalate Buffer

Place 50 ml. of the potassium biphthalate solution in a 200-ml. volumetric flask, add the specified volume of the sodium hydroxide solution, then add water to volume.

pH	4.2	4.4	4.6	4.8	5.0	5.2	5.4	5.6	5.8
NaOH, ml.	3.0	6.6	11.1	16.5	22.6	28.8	34.1	38.8	42.3

Phosphate Buffer

Place 50 ml. of the monobasic potassium phosphate solution in a 200-ml. volumetric flask, add the specified volume of the sodium hydroxide solution, then add water to volume.

pH	5.8	6.0	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.0
NaOH, ml.	3.6	5.6	8.1	11.6	16.4	22.4	29.1	34.7	39.1	42.4	44.5	46.1

Alkaline Borate Buffer

Place 50 ml. of the boric acid and potassium chloride solution in a 200-ml. volumetric flask, add the specified volume of the sodium hydroxide solution, then add water to volume.

pH	8.0	8.2	8.4	8.6	8.8	9.0	9.2	9.4	9.6	9.8	10.0
NaOH, ml.	3.9	6.0	8.6	11.8	15.8	20.8	26.4	32.1	36.9	40.6	43.7

CHLORIDE AND SULFATE LIMIT TESTS

The following limit tests are provided as general procedures for use where limits for chloride and sulfate are specified in the individual monographs.

Perform the tests and the controls in glass cylinders of the same diameter and matched as closely as practicable in other respects. Use the same quantities of the same reagents for both the solution under test and the control solution containing the specified volume of chloride or sulfate. If after acidification the solution is not perfectly clear, filter it through a filter paper that gives negative tests for chloride and sulfate. Add the precipitant, silver nitrate T.S. or barium chloride T.S. as required, to both the test solution and the control solution in immediate sequence.

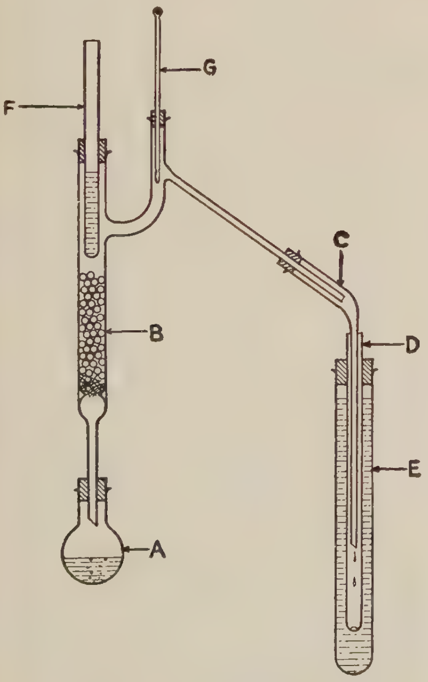
Where the individual monograph calls for applying the test to a specific volume of a solution of the substance, and the limit for chloride or sulfate corresponds to 0.2 ml. or less of 0.02 *N* hydrochloric or sulfuric acid, respectively, apply the test to the solution without further dilution. In such cases maintain the same volume relationships for the control solution as specified for the solution under test. In applying the test to the salts of heavy metals, which normally show an acid reaction, omit the acidification and do not neutralize the solution. Dissolve bismuth salts in a few ml. of water and 2 ml. of nitric acid before treating with the precipitant.

Chloride—Dissolve the specified quantity of the substance under test in 30 to 40 ml. of water, or, where the substance is already in solution, add water to make a total volume of 30 to 40 ml. and, if necessary, neutralize the solution to litmus with nitric acid. Add 1 ml. each of nitric acid and of silver nitrate T.S., and sufficient water to make 50 ml. Mix, allow to stand for 5 minutes protected from direct sunlight, and compare the turbidity, if any, with that produced in a solution containing the volume of 0.02 *N* hydrochloric acid specified in the monograph.

Sulfate—Dissolve the specified quantity of the substance under test in 30 to 40 ml. of water, or, where the substance is already in solution, add water to make a total volume of 30 to 40 ml. and, if necessary, neutralize the solution to litmus with hydrochloric acid. Add 1 ml. of diluted hydrochloric acid, 3 ml. of barium chloride T.S., and sufficient water to make 50 ml. Mix, allow to stand for 10 minutes, and compare the turbidity, if any, with that produced in a solution containing the volume of 0.02 *N* sulfuric acid specified in the monograph.

CHLOROFORM DETERMINATION

This method is intended for the determination of chloroform in mixtures with alcohol or with alcohol and water when specified in individual NF monographs. The apparatus required consists of a 100-ml. extraction flask, *A;* a dephlegmator, *B;* an adapter, *C;* a carbon tube (Eggertz Color Comparison Tube), *D,* having a capacity of 30 ml. and graduated to 0.1 ml.; and a water jacket, *E,* for the carbon tube. The dephlegmator consists of a glass tube of 25 mm. internal diameter and 27.5 cm. in length, which is sealed at one end to a glass tube of 6 mm. internal diameter and 10 cm. in length, the end of which is ground to an angle of 45°. At a distance of 25 mm. above the joint the larger tube is indented at four points equally spaced about its circumference, the indentations nearly meeting in the center of the tube. The top of the tube is finished with a ring. A side tube of 12 mm. internal diameter is sealed to the larger tube at a point 87 mm. below the top, and this tube is bent vertically upward with a smooth curve so that the distance between the opposing walls of the tubes is 50 mm. and the top of the side tube 50 mm. above the top of the larger tube. A delivery tube of 6 mm. internal diameter and 22.5 cm. in length is sealed to the side tube about midway of its length, the delivery tube forming an angle of about 120° to the upward extension of the side tube. The top of the main tube is closed with a 1-hole cork stopper, the surface of which has been lightly charred, which carries a glass refluxing tube, *F,* of 12 mm. internal diameter and 25 cm. in length, sealed at the lower end, and extending to about 12 mm. below the entrance to the side tube, the refluxing tube being filled to about one-half its length with alcohol. A pledget of glass wool is placed upon the indentations in the main tube and the tube then filled to a height of about 12 cm. with glass beads. The open end of the side tube is closed with a lightly charred cork carrying a thermometer, *G,* graduated to 100°. The delivery tube is attached by a lightly charred cork to a bent adapter, the extension of which is bent vertically downward and extends about two-thirds of the distance to the bottom of the carbon tube. The carbon tube is supported by means of a 1-hole stopper in a test tube of about 37 mm. internal diameter and 30 cm. in length, which is to be filled with a mixture of finely crushed ice and water during the distillation.



Chloroform Determination Apparatus

Place 50 ml. of water in the extraction flask and add the volume of sample specified in the individual monograph by holding the tip of the pipet just below the surface of the water. Connect the flask to the dephlegmator by a 1-hole cork stopper, the surface of which has been lightly charred after boring. Fill the refluxing tube to about one-half its depth with alcohol. Place 5 ml. of water in the carbon tube, connect the dephlegmator with an adapter which extends to within about 25 mm. of the water in the carbon tube, and surround the carbon tube with a mixture of ice and water. Lower the carbon tube as necessary during the distillation to keep the end of the adapter above the liquid in the carbon tube.

Heat the liquid in the flask until it boils gently, and continue the heating until no more chloroform is seen to sink through the water in the carbon tube and the interior walls of the dephlegmator and adapter are free from globules. The temperature recorded by the thermometer must not rise above 78° during the distillation. When distillation of the chloroform is complete, fill the carbon tube to the 30-ml. mark, swirl it vigorously to dissolve any alcohol carried over with the chloroform, and then tap the carbon tube sharply on the desk to collect any globules of chloroform adhering to the walls. Finally, place the carbon tube in a bath of water at 25°, and read the volume of chloroform when that temperature has been attained.

CHROMATOGRAPHY

For National Formulary purposes, chromatography is defined as a procedure by which essential drug principles and other substances encountered in pharmaceuticals are separated by fractional extraction, or adsorption, or ion exchange on a porous solid, by means of flowing liquid or vapor solvents. The materials thus obtained can be identified or determined by analytical methods. The four types of chromatography generally employed in the tests and assays are column, paper, thin-layer, and gas chromatography. Paper and thin-layer chromatography are usually more useful for identification tests because of their specificity and convenient suitability for small quantities. Adsorbants other than paper are usually porous adsorbent materials, such as activated alumina, silicic acid or silica gel, diatomaceous earth, and synthetic resins, alone or mixed or as supports for other materials. Gas chromatography requires more elaborate equipment, but it is useful as a quantitative as well as a qualitative procedure.

Column Chromatography

Adsorption Chromatography—The adsorbant (such as activated alumina, silica gel, calcined diatomaceous silica, chromatographic purified siliceous earth, etc.) as a dry solid or as a slurry is packed into a glass or quartz tube of suitable dimensions (see page 8) having a restricted outflow orifice. A solution of the drug in a small amount of solvent is added to the top of the column and allowed to flow into the adsorbent. The drug principles are quantitatively removed from the solution and are adsorbed in a narrow transverse band at the top of the column. As additional solvent is allowed to flow through the column, either by gravity or by application of air pressure, each substance progresses down the column at a characteristic rate resulting in a spatial separation to give what is known as the *chromatogram*. The rate of movement for a given substance is affected by several variables, including the adsorptive power of the adsorbent, the nature of the solvent, and the temperature of the chromatographic system.

If the separated compounds are colored or if they fluoresce under ultraviolet light, the adsorbent column may be extruded and, by transverse cuts, the appropriate segments may then be isolated. The desired compounds are then extracted from each segment with a suitable solvent. If the compounds are colorless, they may be located by painting or spraying the extruded column with color-forming reagents. Where radioactive substances are chromatographed, they may be detected by means of a Geiger-Müller counter or similar sensing and measuring instruments.

The "flowing chromatogram" is used quite extensively. With this type, solvents are allowed to flow through the column until the separated drug appears in the effluent solution, known as the "eluate." The drug may be determined in the eluate by titration or by a spectrophotometric or colorimetric method, or the solvent may be evaporated, leaving the drug in more or less pure form. If a second drug principle is involved, it is eluted by continuing the first solvent or by passing a solvent of stronger eluting power through the column.

A modified procedure for adding the mixture to the column is sometimes employed. The drug, in a solid form, and, as in the case of a powdered tablet, without separation from the excipients, is mixed with some of the adsorbent and added to the top of a column. The subsequent flow of solvent moves the drug down the column in the manner described.

Partition Chromatography—In partition chromatography the substances to be separated are partitioned between two immiscible liquids one of which, the immobile phase, is usually adsorbed on a solid adsorbent, thereby presenting a very large surface area to the flowing solvent or mobile phase. The exceedingly high number of liquid-liquid contacts allows an efficiency of separation not achieved in ordinary liquid-liquid extraction.

In practice, partition chromatography is carried out in much the same manner as adsorption chromatography; *i.e.*, the mixture, dissolved in a small amount of the solvent, is added to the top of the column, and development and elution are accomplished with flowing solvents. The mobile solvent usually is saturated with the immobile solvent before use.

In some cases it is helpful to add the drug dissolved in the immobile solvent to a small amount of adsorbent, transferring this mixture to the top of the column.

Gas Chromatography

Gas chromatography denotes the technique in which the moving phase is a gas. In other forms of chromatography the moving phase is a liquid. The stationary phase in chromatographic techniques is either a solid or a liquid, or a combination of both.

In gas-liquid chromatography, the stationary liquid phase is immobilized as a thin film on a finely divided, inert solid support, such as chromatographic siliceous earth, crushed firebrick, glass beads, or even the inner wall of a small diameter tube. The support should not retard the passage of the drug or other components through the tube. If the latter is filled with the liquid-covered, finely divided solid, it is called a packed column (usually 3 to 6 mm. in internal diameter). If the inner wall of a small-diameter tube (usually 0.25 to 0.5 mm. in internal diameter) is coated with the liquid, it is called an open tubular or capillary column. In some techniques, the inner wall of such capillary tubing is coated with a finely divided solid support on which the liquid phase is placed, so that the difference between the two main types of gas chromatography columns is becoming less distinct.

In gas-solid chromatography, the identical situation holds except that the liquid phase is absent and the solid is an active adsorbent, such as alumina, silica gel, or carbon.

In gas-liquid chromatography, the mobile gas phase continuously moves over the stationary phase. When a vaporized substance is introduced into the gas stream at the head of the column, it is swept into the column and undergoes distribution between the gas and liquid phases. The behavior of a solute in such a partition process is most conveniently defined by a dimensionless factor called the partition ratio, k. The partition ratio is simply the ratio of the amount of solute dissolved in the stationary phase to the amount of solute dissolved in the mobile phase; *i.e.*,

$$k = \frac{\text{amount of solute in liquid phase}}{\text{amount of solute in gas phase}} \qquad (1)$$

and, for compendial purposes, k is assumed constant throughout the column. The partition ratio is related also to the time that a solute spends in each of the phases; so that

$$k = \frac{\text{time in liquid phase}}{\text{time in gas phase}} \qquad (2)$$

Also, the partition ratio, k, can be related to the t_R factor (retention time). Obviously, the greater the total amount of liquid phase in the column, the more solute will dissolve in it and the greater will be the partition ratio by Equation 1. Similarly, an increase in the amount of liquid phase results in increased residence time in that phase, and the partition ratio increases (Equation 2). As has been noted, the gas phase simply serves to move the solute through the column between excursions into the liquid phase. Consequently, it is important to note that all solutes spend the same time in the gas phase in any particular column.

It is apparent that the value of the partition ratio, and, therefore, the time in the column depends upon the following solubility considerations: (a) the specific solute; (b) the specific liquid phase (solvent); (c) the amount of liquid phase; (d) the temperature; and (e) the gas flow rate. Therefore, a partition ratio exists for each column, solute, and temperature; and in order to reproduce the behavior of a particular solute, almost every experimental factor must be carefully reproduced, as is true of all other chromatographic techniques.

Apparatus—The basic apparatus required to perform gas chromatographic separations is quite simple. *Carrier gas*, usually available in compressed form in a cylinder fitted with a suitable pressure-reducing valve, is conducted from the cylinder into a flow meter where the flow rate is determined. This step is necessary in order to reproduce a particular flow condition that has been found the most satisfactory for the resolution of a particular mixture. Helium is often selected because it is inert and has a high thermal conductivity relative to that of most organic compounds. Since solutes to be chromatographed must be in the vapor phase, the *injection port* is heated to a temperature high enough to ensure rapid vaporization but not to cause thermal degradation of the compound. Liquids, solutions, and gas samples are almost always injected by syringe through a silicone rubber septum in the injection port. In many instruments, the sample is injected directly onto the column packing, alternatively, the sample vapor mixes instantaneously with the flowing carrier gas and is swept into the *column*. It is in the column that the different components of the vaporized sample are separated by virtue of their different interactions with the stationary column *packing*. The tubing which contains the packing commonly is made either of metal or glass. Glass tubing is the more inert and may be specified in individual monographs. The column also must be maintained at a selected temperature, which determines the time for the passage of the sample components, and, to a degree, the resolution and efficiency obtained with the particular column. As the components emerge individually from the end of the column, they enter a differential-type *detector*, which indicates the amount of drug or component leaving the column. Control of the detector temperature to prevent condensation is essential. Two types of detector are used most in pharmaceutical analysis, thermal conductivity and flame ionization. The choice of detector is specified within the individual monographs. A variety of more specialized detectors is available. The detector is coupled to a suitable automatic recording device, such as a recording potentiometer. The resulting record is a signal-time plot, which may then be used to determine the identities and concentrations of the components. The usual detectors emit a signal proportional to the concentration of the solute in the carrier gas as it leaves the column. Thus, the chromatogram for each drug appears as a bell-shaped (Gaussian) peak on a time axis. A detector arrangement that provides such a signal is called a differential-type detector, and the resulting curves accurately represent the distribution process as it has occurred during the residence time of the solutes in the column.

Procedure—Gas chromatography is a separation method only, but with proper calibration, it can be used to identify compounds. To achieve qualitative analysis, the retention time or volume of the peak maximum of a known pure compound must be determined. Then, when a peak appears at that same time or volume under the same experimental conditions, the certainty of identification is quite high. Alternatively, the individual components may be collected in a cold trap as they emerge from the column and be subjected to independent analysis by instrumental or chemical methods. Mass spectrum or radioactivity of eluted solutes may be monitored with some equipment. The elution time or volume for air is an important quantity, since it corresponds closely to the gas space in the column. This value is frequently used to obtain absolute and relative retention values for characterisation of compounds. Compounds may be identified best by means of their relative retention, α, *i.e.*,

$$\alpha = \frac{r_2 - r_a}{r_1 - r_a} \qquad (3)$$

where r_2 is the retention from zero time or injection point (as time, volume, or distance on the chromatogram) to the peak apex of the desired drug and r_1 is the same for a standard material determined with the same column and temperature, and r_a is the retention for an inert component, such as air, which is not retarded in its passage through the column. Using these retention symbols, the partition ratio for the compounds having a retention of r_2 is:

$$k_2 = \frac{r_2}{r_a} - 1 \qquad (4)$$

Tables of α may be prepared, stating the standard material used to obtain x_1, which can then be referred to for identification purposes. Retention times measured from injection alone are used commonly, especially in conjunction with flame ionization detectors which respond neither to air nor water.

As a measure of efficiency of the separation of two components in a mixture, the resolution factor, R, is determined as

$$R = \frac{2(t_R - t_R')}{1.669(W_{h/2} + W'_{h/2})} \qquad (5)$$

in which t_R and t_R' are the respective retention times of two components of the mixture, and $W_{h/2}$ and $W'_{h/2}$ are the corresponding extrapolated peak widths measured in units of time on the chromatogram at a distance one-half of the way from the apex to the base of the peak.

Quantitative results can be obtained from the areas under the peaks. The areas are determined by means of an automatic integrator, a planimeter, or by triangulation. For systems where equivalent accuracy can be obtained, peak heights may be substituted for areas. Peak area measurement is less accurate for small peaks and those having short retentions.

Area percentages, $\% A_i$, or a/a, of individual species within a chromatogram are used in purity analysis and are equal to 100-times the ratio of the peak area of the species, A_i, to the sum, ΣA_i, of all the areas of the peaks in the chromatogram. Where the individual components and response factors are known, measure the area of each peak and convert this to mass of sample component by multiplying the peak area by a sensitivity factor for that component. Where response factors of the various components are nearly equal, the product of retention time and peak height may be substituted for peak area measurements to minimize graphical error. Where the identity of other components is known, calibration curves may be based on relative peak heights, such as in water content limit tests for solvents.

Assays require quantitative comparison of one chromatogram to another, and control of the sample size injected is a major source of error. Use of an internal standard eliminates this error and the ratio of peak heights of the species of interest to the standard are compared from one chromatogram to another. The internal standard chosen must not coincide with any other peak in the chromatogram. When the internal standard is chemically similar to the compound to be analyzed (analyte), minor variation in column and detector parameters are controlled also. In some cases the internal standard may be carried through the procedure prior to gas chromatography to control other quantitative aspects of the procedure.

Special grade solvents are required sometimes, especially where extensive concentration of analytes is necessary prior to chromatography. Such chromatographic grade reagents may be specified within individual monographs. Most compounds are polar molecules with reactive groups. Successful chromatography may require the conversion of the compound to a more volatile or less polar derivative by treating reactive groups with appropriate reagents.

A quantity of solute may be adsorbed within the system and this would be reflected in the failure of the calibration curve to pass through zero, terminating rather along the abscissa. This effect may contribute error, particularly for the measurement of small sample sizes using a single reference point. At high sample concentrations, the solute may overload the liquid phase leading to relative loss of peak height or symmetry. Before accepting any column for assay purposes, a calibration curve should be constructed to control these errors prior to the use of the single standard sample size used in most compendial assays.

Columns—Pharmaceutical analyses usually employ packed columns and, ideally, only the packing influences the movement of solutes through the system under given conditions. Various dimensions of columns are used, normally 0.6–1.8 meter in length and internal diameters of 3–6 mm. Low-capacity columns, about 5% w/w or less of liquid phase on the solid support, are preferred for analytical use. High-capacity columns, such as 20% w/w liquid loadings, are used normally for such determinations as water content of solvents. The desired capacity influences the choice of solid supports.

Support materials are available in various mesh size ranges, with 80–100 and 100–120 mesh most commonly used with 3 to 6 mm. diameter columns. The support material should be as inert as possible, particularly for polar drugs being chromatographed on low capacity, low-polarity liquid phase columns. Reactive supports can result in decomposition, rearrangement or peak tailing of the solute. Acid-washed, flux-calcined diatomaceous earth has become the most used support material for drugs. Reactivity of the support is reduced by treatment with a silanizing reagent prior to coating with liquid phase. Some available supports receive an additional alkaline wash, but residual alkali decomposes certain liquid phases. Polyaromatic porous resins are available which do not require coating with liquid phase and such packings are specified in individual monographs.

Liquid phases are drawn from a wide range of chemical classes. Polyethylene glycols, high molecular weight esters and amides, hydrocarbons and silicone gums and fluids are used most commonly. Silicone gums and fluids are polysiloxanes substituted normally by methyl, phenyl, nitrile, vinyl, or fluoroalkyl groups, or mixtures of these. In all cases, care should be taken to obtain batches selected for use in gas chromatography. At operating temperatures, even these materials have sufficient vapor pressure to result in gradual loss of liquid phase by bleeding. Some phases are characterized by extremely low bleed rates at operating temperatures and, in such cases, columns may be rejuvenated by repacking the first 10 to 15 cm. to remove injection residues.

Columns should be conditioned by operating until stable at a temperature higher than that in the monograph. In the case of thermally stable methyl and phenyl-substituted polysiloxanes, the following special curing sequence has been found to increase inertness and efficiency: maintain the column at 250° for an hour with helium flowing to remove oxygen and solvents, stop the flow of helium and heat at about 340° for 4 hours, lower the temperature to 250°, and condition with helium flowing until stable. A suitable test for support inertness, necessary with these low polarity liquid phases, is the delivery of a single symmetric peak for injected cholesterol with no evidence of decomposition.

Packed, cured and conditioned columns should be tested prior to acceptance for assay use. The peaks should be symmetric. Carrier gas flow and temperature should be adjusted for optimum results and assay time. Guides to column parameters are included in the monographs. A calibration curve should be prepared for the intended drugs, concentrations and operating conditions. In some cases, resolution and column efficiency may be specified within a monograph. Column efficiency is expressed in terms of theoretical plates, n, calculated by the formula:

$$n = 5.54 \left(\frac{t_R}{W_{h/2}}\right)^2 \qquad (6)$$

where t_R and $W_{h/2}$ are measured in the same units.

Paper Chromatography

In paper chromatography the adsorbent is a sheet of paper of suitable texture and thickness. Chromatographic separation may proceed through the action of a single liquid phase in a process analogous to adsorption chromatography in columns; or two immiscible solvents may be employed for partition chromatography on paper. In the latter process, the mobile phase moves slowly over the stationary phase which covers the fibers of the paper or forms a complex with them. The ratio of the distance traveled on the paper sheets by a given compound to the distance traveled by the front of the mobile phase, from the point of application of the test substance is designated as the R_f value of the compound. The ratio of the distance traveled by a given compound to that of a reference substance constitutes the R_r value.

Use of Reference Substances in Identity Tests—Absolute R_f values are difficult to establish, since the observed R_f values vary with the experimental conditions. They are, however, very useful in tentatively identifying chemical compounds. A more definite identification is accomplished by using as a reference substance an authentic specimen of the compound in question.

For this purpose three chromatograms are prepared on the same sheet of paper: one from the substance to be identified, one from the authentic specimen, and one from a mixture of nearly equal amounts of the substance to be identified and the authentic specimen. Each chromatogram contains approximately the same quantity by weight of material to be chromatographed. If the substance to be identified and the authentic specimen are identical, all three chromatograms will have the same R_f value, and the mixed chromatogram yields a single spot; *i.e.*, R_r is 1.0.

Location of the Spots—The spots produced by the chromatographed materials may be located by: (1) direct inspection if the compounds are visible under white or ultraviolet light, (2) inspection in white or ultraviolet light after treatment of the sheets with reagents that will make the spots visible (reagents are most conveniently applied with an atomizer), (3) use of a Geiger-Müller counter or autoradiographic techniques in the case of the presence of radioactive substances, or (4) evidence resulting from stimulation or inhibition of bacterial growth by placing strips or cutouts on inoculated media.

Descending Chromatography—Separation of substances by descending chromatography is accomplished by allowing the mobile phase to flow downward on the chromatographic sheet.

Apparatus—The essential equipment for descending chromatography consists of the following: a *vapor-tight chamber* provided with inlets for addition of solvent or for releasing internal pressure. The chamber is constructed preferably of glass, stainless steel, or porcelain and is so designed as to permit observation of the progress of the chromatographic run without opening the chamber. Tall glass cylinders are convenient if they are made vapor-tight with suitable covers and a sealing compound.

A *rack of corrosion-resistant material* about 5 cm. shorter than the inside height of the chamber. The rack serves as a support for solvent troughs and for antisiphoning rods which, in turn, hold up the chromatographic sheets.

One or more *glass troughs* capable of holding a volume of solvent greater than that needed for one chromatographic run. The troughs must also be longer than the width of the chromatographic sheets.

Heavy glass antisiphoning rods to be supported by the rack and running outside of, parallel to, and slightly above the edge of the glass trough.

Chromatographic sheets of special filter paper cut to a length approximately equal to the height of the chamber. The sheet is at least 2.5 cm. wide but not wider than the length of the trough. A fine pencil line is drawn horizontally across the filter paper at a distance from one end such that, when the sheet is suspended from the antisiphoning rods with the upper end of the paper resting in the trough and the lower portion hanging free into the chamber, the line is located a few cm. below the rods. Care is necessary to avoid contaminating the paper by excessive handling or by contact with dirty surfaces.

Procedure—The substance or substances to be analyzed are dissolved in a suitable solvent. Convenient volumes of the resulting solution, normally containing 1 to 20 mcg. of the compound, are placed in 6- to 10-mm. spots along the pencil line not less than 3 cm. apart. If the total volume to be applied would produce spots of a diameter greater than 6 to 10 mm., it is applied in separate portions to the same spot, each portion being allowed to dry before the next is added.

The spotted chromatographic sheet is suspended in the chamber by use of the antisiphoning rod and an additional heavy glass rod which holds the upper end of the sheet in the solvent trough. The bottom of the chamber is covered with a mixture containing both phases of the prescribed solvent system. It is important to ensure that the portion of the sheet hanging below the rods is freely suspended in the chamber without touching the rack or the chamber walls or the fluid on the bottom of the chamber. The chamber is sealed to allow equilibration (saturation) of the chamber and the paper with the solvent vapor. Any excess pressure is released as necessary. For large chambers, equilibration overnight may be necessary.

A volume of the mobile phase in excess of the volume required for complete development of the chromatogram is saturated with the immobile phase. After equilibration of the chamber, the prepared mobile solvent is introduced into the trough through the inlet. The inlet is closed and the mobile solvent phase is allowed to travel down the paper the desired distance. Precautions must be taken against allowing the solvent to run down the sheet when opening the chamber and removing the chromatogram. The location of the solvent front is quickly marked, and the sheets are dried.

The chromatogram is observed and measured directly or after suitable development to reveal the location of the spots of the isolated drug or drugs.

Ascending Chromatography—In ascending chromatography the lower edge of the sheet (or strip) is dipped into the mobile phase, to permit the mobile phase to rise on the chromatographic sheet.

Apparatus—The essential equipment for ascending chromatography is substantially the same as that described under *Descending Chromatography.*

Procedure—The test materials are applied to the chromatographic sheets as directed under *Descending Chromatography.* Enough of both phases of the solvent mixture to cover the bottom of the chamber is added. Empty solvent troughs are placed on the bottom of the chamber, and the chromatographic sheets are suspended so that the end near which the spots have been added hangs free inside the empty trough.

The chamber is sealed, and equilibration is allowed to proceed as described under *Descending Chromatography.* Then the solvent is added through the inlet to the trough in excess of the solvent required for complete moistening of the chromatographic sheet. The chamber is resealed. When the solvent front has reached the desired height, the chamber is opened and the sheet is removed, the location of the solvent front is quickly marked, and the sheets are dried.

Small cylinders may be used without troughs so that only the mobile phase is placed on the bottom. The chromatographic sheet is suspended during equilibration with the lower end just above the solvent and chromatography is started by lowering the sheet so that it touches the solvent.

Thin-Layer Chromatography

Thin-layer chromatography is used for the rapid separation of compounds by means of a uniform layer of finely powdered material applied to a glass plate. The coated plate can be considered as an "open chromatographic column" and the separations achieved may be based upon adsorption, partition, or a combination of both effects, depending on the particular type of support, its preparation, and its use with different solvents. Thin-layer chromatography on ion exchange films can be used for the fractionation of polar compounds. The R_f values obtained by thin-layer chromatography are less reproducible than those obtained by paper chromatography. For this reason it is always necessary to prepare chromatograms of authentic specimens or reference standards, preferably in varied quantities, alongside the chromatogram of the sample. Presumptive identification can be effected by observation of 2 spots of identical R_f value and about equal magnitude. A visual comparison of the size of the spots may serve for semiquantitative estimation. More accurate quantitative measurements can be made by densitometry or careful removal of the spots from the plate, followed by elution with a suitable solvent and spectrophotometric measurement. For two-dimensional thin-layer chromatography, the chromatographed plate is turned at a right angle and again chromatographed, usually in another chamber equilibrated with a different solvent system.

Apparatus—A suitable apparatus and materials for thin-layer chromatography consist of the following: *glass plates,* of uniform thickness throughout their entire areas, measuring 20 × 20 cm.; with two plates measuring 5 × 20 cm. to serve as end plates. Other convenient size plates may be used. An *aligning tray* to furnish a flat surface upon which to align and rest the plates during the application of the adsorbent. A suitable tray measures 122 × 23 cm., with one raised end and side against which the plates can be held in place. A *storage rack* to hold the prepared plates during the drying period or for transportation of plates. It should accommodate about 10 plates with fixed spacing between plates and its dimensions should permit convenient placement in a drying oven.

The *adsorbent* may consist of finely divided adsorbent materials for chromatography. The adsorbent can be applied directly to the glass plate or it can be bonded to the plate by means of plaster of Paris (at a ratio of 5 to 15 percent) or with starch paste. The former will not yield as hard a surface as will the starch, but it is not affected by strongly oxidizing spray reagents.

A *spreader* in the form of a precision-machined trough with a lengthwise slit at the bottom and of such weight that, when moved over the glass plate, it will apply a uniform layer of adsorbent, 250 μ thick, over the entire surface of the plate. Other thicknesses might be desirable in some procedures, and an adjustable spreader would be particularly useful in such cases.

A glass *developing chamber* which can efficiently accommodate 2 glass plates. It should have a smoothly and evenly ground top which can be properly closed and sealed with a glass cover with the aid of a *sealing compound,* such as a high vacuum grease. A stainless steel *plate-support rack* which can support two glass plates, back to back, within the developing chamber with the lid in place.

A *template* device (generally made of plastic) to aid in placing the sample spots at definite intervals, to enable marking distances as needed, and also to aid in labeling the plates.

A graduated *micropipet* capable of delivering 10-μl. quantities. Total quantities of sample and standard solutions are specified in the individual monographs.

A *reagent sprayer* device which will emit a fine spray and will not itself be attacked by the reagent.

The *solvent, standard solution, sample solution,* and *reagents* are specified in the individual monographs.

An *ultraviolet light source* suitable for observations with short (254 mμ) and long (360 mμ) ultraviolet wavelengths.

Procedure—Clean the glass plates by immersion in chromic acid cleansing mixture, rinse them with copious quantities of water until the water runs off the plates without leaving any visible water or oily spots, then dry with a clean towel. [Note: It is very important that the plates be completely free of lint or dust when the adsorbant is applied.]

Arrange the plate or plates on the aligning tray, place a 5 × 20-cm. plate adjacent to the front edge of the first square plate and another 5 × 20-cm. plate adjacent to the rear edge of the last square and secure all the plates so they will not slip during the application of the adsorbent. Position the spreader on the end plate opposite to the raised end of the aligning tray. Mix 1 part of adsorbent with 2 parts of water—or in the ratio suggested by the supplier—by shaking vigorously for 30 seconds in a glass-stoppered conical flask, and transfer the slurry to the spreader. (Usually 30 g. of adsorbent and 60 ml. of water are sufficient for five 20 × 20-cm. plates. The application must be complete within 2 minutes of addition of the water as the mixture begins to harden after this period.) Draw the spreader smoothly over the plates toward the raised end of the aligning tray, and remove the spreader when it is on the end plate next to the raised end of the aligning tray. (Wash away all traces of adsorbent from the spreader immediately after use.) Allow the plates to remain undisturbed for 5 minutes, then transfer the square plates, layer side up, to the storage rack and dry at 105° for 30 minutes. [Note: When the plates are dry, allow them to cool to room temperature and inspect the uniformity of the distribution and the texture of the adsorbent layer; transmitted light will show uniformity of distribution and reflected light will show uniformity of texture.] Store the satisfactory plates in a suitable desiccator.

Place 2 filter paper wicks, 18 cm. high and as wide as the length of the developing chamber, into the chamber, add about 100 ml. of the solvent (sufficient to have a depth of 0.5 cm. to 1 cm. at the bottom of the chamber), seal the cover to the top of the chamber and allow the system to equilibrate; the wicks must become completely wet. Alternatively, the chamber may be completely lined with filter paper. In either case, the filter paper must dip into the solvent at the bottom of the chamber. Where vapor saturation of the chamber by these methods is undesirable it is indicated in the individual monograph.

Apply the *Sample solution* and the *Standard solution,* as directed in the individual monographs at points about 1.5 cm. apart and about 2 cm. from the lower edge of the plate (the lower edge is the first part over which the spreader moved in the application of the adsorbent layer), and allow to dry. [Note: The template will aid in determining the spot points and the 10-cm. distance through which the solvent front should pass.]

Place a mark 10 cm. above the spot point. Arrange the plate on the supporting rack (sample spots on the bottom) and introduce the rack into the developing chamber. The solvent in the chamber must reach the lower edge of the adsorbant, but do not allow the spot points to be immersed. Seal the cover into place with the sealing compound and maintain the system until the solvent ascends to a point 10 to 15 cm. above the initial spots, this commonly requiring about 15 minutes to 1 hour. Remove and air dry the plates, and observe first under shortwave ultraviolet light (254 mμ) then under longwave ultraviolet light (360 mμ). Measure and record the distance of each spot from the point of origin, and indicate for each spot the wavelength under which it was observed. If further directed, spray the spots with the reagent specified in the monograph, observe, and compare the sample with the standard chromatogram. Calculate R_f values as described under *Paper Chromatography,* page 789.

COBALAMIN ASSAY—RADIOTRACER METHOD

All radioactive determinations required by this method should be made with a suitable counting assembly over a period of time optimum for the particular counting assembly used. All procedures should be performed in replicate to obtain the greatest accuracy.

Cyanocobalamin Tracer Reagent—Dilute an accurately measured volume of a solution of radioactive cyanocobalamin* with sufficient water to yield a solution having a radioactivity between 500 and 5000 counts per minute per ml. Add 1 drop of cresol per liter of solution prepared, and store in a refrigerator.

Standardization—Prepare a solution in water of a weighed quantity of USP Cyanocobalamin Reference Standard to contain 20 mcg. to 50 mcg. in each ml. Perform the entire assay on a 10.0-ml. portion of this solution, proceeding as directed under *Assay Preparation,* beginning with "Add water to make a measured volume. . . ."

Cresol-Carbon Tetrachloride Solution—Mix equal volumes of carbon tetrachloride and freshly distilled cresol.

Phosphate-Cyanide Solution—Dissolve 100 mg. of potassium cyanide in 1000 ml. of a saturated solution of dibasic sodium phosphate, and mix well.

Butanol-Benzalkonium Chloride Solution—Dilute 3 volumes of 17 percent benzalkonium chloride solution with 1 volume of water, and mix with 36 volumes of 1-butanol.

Alumina-Resin Column—Place a pledget of glass wool in the bottom of a constricted glass tube such as a 50-ml. buret. With the tube held in an upright position, add a volume of a slurry of ion-exchange resin (see page 919), in water sufficient to give a column of settled resin 7 cm. in height. When the solid has settled somewhat, allow the water to drain so that there is only 1 cm. of liquid above the resin column, and tamp the resin lightly. Then add a volume of a slurry of anhydrous alumina (not acid washed) in water sufficient to increase the height of the settled column to 10 cm., and allow the water to drain to about 1 cm. from the top of the alumina. Add a pledget of glass wool, and wash the column, using a total of 50 ml. of water, and again draining to within 1 cm. of the top of the column. Prepare a fresh column for each determination.

Assay Preparation—Transfer to a beaker a weighed quantity or measured volume of the preparation to be assayed, equivalent in vitamin B_{12} activity to that of 200 to 500 mcg. of cyanocobalamin. Add water to make a measured volume of not less than 25 ml., then add 5.0 ml. of *Cyanocobalamin Tracer Reagent.* Add, while working *under a hood,* 5 mg. of sodium nitrite and 2 mg. of potassium cyanide for each ml. of the resulting solution. Adjust the solution to approximately pH 4 with diluted hydrochloric acid, and heat on a steam bath for 15 minutes. Cool, and adjust the pH to between 7.6 and 8.0 with sodium hydroxide T.S. Centrifuge or filter to remove any undissolved solids.

Procedure—Transfer the *Assay Preparation* to a 250-ml. centrifuge bottle, add 10 ml. of *Cresol-Carbon Tetrachloride Solution,* suitably close the bottle with a glass, polyethylene or foil-wrapped rubber stopper, shake vigorously for 2 to 5 minutes, and centrifuge. Remove and save the lower, solvent layer. Repeat the extraction using a 5-ml. portion of *Cresol-Carbon Tetrachloride Solution,* and combine the lower, solvent-layer extracts in a centrifuge bottle or separator of 50 to 100-ml. capacity.

Wash the combined extracts with successive, 10-ml. portions of dilute sulfuric acid (1 in 7) until the last washing is practically colorless (two washings usually suffice). During each washing, shake for 2 to 5 minutes, allow the layers to separate, centrifuge if necessary, and discard the acid layer. Wash further with two successive, 10-ml. portions of *Phosphate-Cyanide Solution.* Finally, wash with 10 ml. of water. Discard all of the washings.

To the washed extract add 30 ml. of a mixture of 2 volumes of *Butanol-Benzalkonium Chloride Solution* and 1 volume of carbon tetrachloride. Extract with two successive, 5-ml. portions of water, each time shaking vigorously for 1 minute, centrifuging, and removing and saving the upper, aqueous layer.

Pass the combined aqueous extracts through the *Alumina-Resin Column* at a rate of about 1 ml. per minute, maintaining a 1-cm. layer of liquid on the head of the column by adding water as needed. Discard as much of the forerun as is colorless (usually about 5 ml.), and collect the colored eluate (usually about 10 ml.) in a 50-ml. centrifuge tube or separator containing 0.5 ml. of diluted acetic acid. Extract the eluate by shaking for 2 to 5 minutes with 5 ml. of *Cresol-Carbon Tetrachloride Solution,* and discard the upper, aqueous layer. To the extract add 5.0 ml. of water, 5 ml. of carbon tetrachloride and 10 ml. of 1-butanol. Shake, allow to separate until the upper layer is clear, and remove the upper, aqueous layer.

Determine the absorbance of the aqueous extract at 361 mμ and 550 mμ in a 1-cm. cell with a suitable spectrophotometer, using a tungsten light source. Make the 361 mμ reading using a filter capable of reducing stray light. Calculate the ratio A_{361}/A_{550}: the purity of the aqueous extract is acceptable if the ratio is not less than 3.10 and not more than 3.40. If a ratio outside this range is observed, purify the aqueous extract by repeating the extraction cycle, proceeding as directed in the foregoing paragraph, beginning with "Pass the combined aqueous extracts through the *Alumina Resin Column*. . .," using a fresh column.

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* A solution of cyanocobalamin made radioactive by the incorporation of ^{60}Co is available from Merck and Co., Inc., Rahway, NJ.

If an acceptable absorbance ratio is observed in the aqueous extract, determine the radioactivity in counts per minute using a suitable counter over a period optimum for the particular counting assembly used. Average the results, and correct the average for the observed background radioactivity determined over two or more 30-minute periods.

Calculation—Calculate the efficiency, E, of the extraction process by the formula $E = (C_S - C_b)/(C_R - C_b)$, in which C_S and C_R are the average radioactivity counts per minute for the preparation under assay and the *Cyanocobalamin Tracer Reagent*, respectively, and C_b is the average count per minute of the background. The cobalamin content, expressed in mcg. of cyanocobalamin, of the portion taken for assay is given by the formula $(A_U/A_S) \times (C_S/C_U) \times R$, in which A_U and A_S are the absorbances determined at 361 mμ of the sample and standard solutions, respectively, C_S and C_U are the corrected average radioactivity values, expressed in counts per minute per ml., of the standard and sample solutions, respectively, and R is the quantity, in mcg., of cyanocobalamin in the portion of the standard solution taken.

COMPLETENESS OF SOLUTION

Place the quantity of the substance specified in the individual monograph in a meticulously cleansed, glass-stoppered, 10-ml. glass cylinder approximately 13 × 100 mm. in size. Add a volume of the solvent specified in the monograph or on the label of the product just sufficient to fill the cylinder almost to the neck. Shake gently to effect solution: the solution is not less clear than an equal volume of the same solvent contained in a similar vessel and examined similarly.

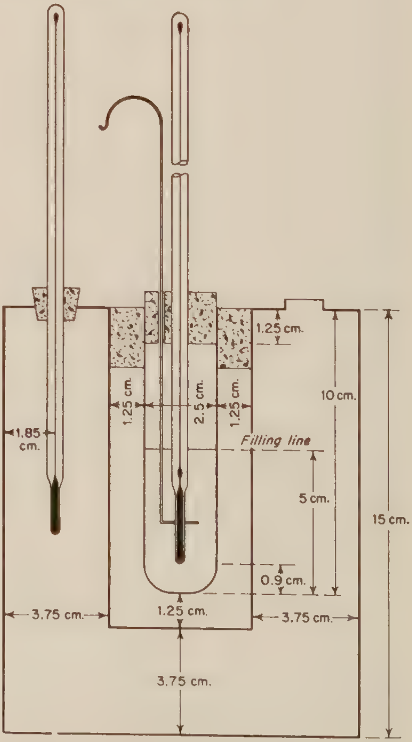
CONGEALING RANGE OR TEMPERATURE

The temperature at which a substance passes from the liquid to the solid state upon cooling is a useful index of purity if heat is liberated when the solidification takes place. The method for determining congealing temperatures set forth here is applicable to substances that melt between −20° and 150°, the range of the thermometer used in the bath. The congealing or solidification temperature is that point at which there exists a mixture of the liquid (fused) phase of a substance and a small but increasing proportion of the hardened or solid phase. It is to be distinguished from the freezing point, which is the temperature at which the liquid and solid phases of a substance are in equilibrium.

Apparatus—Assemble an apparatus similar to that illustrated, in which the container for the substance is a 25 × 100-mm. test tube. This is provided with a suitable, short-range thermometer (see page 880) suspended in the center, and a wire stirrer, about 30 cm. long, bent at its lower end into a horizontal loop around the thermometer.

The sample container is supported, by means of a cork, in a suitable water-tight cylinder about 50 mm. internal diameter and 11 cm. in length. The cylinder, in turn, is supported in a suitable water bath sufficient to provide at least a 37-mm. layer of water surrounding the sides and bottom of the cylinder. The outside water bath is provided with a Type I thermometer.

Procedure—Melt the substance, if a



Congealing Temperature Apparatus

solid, at a temperature not more than 20° above its expected congealing point, and pour it into the test tube to a height of 50 mm. Assemble the apparatus with the bulb of the test tube thermometer immersed halfway between the top and bottom of the sample in the test tube. Fill the water bath to within 12 mm. of the top with water at a temperature 4° to 5° below the expected congealing point.

In case the substance is a liquid at room temperature, carry out the determination using a bath temperature about 15° below the expected congealing point.

When the sample has cooled to about 5° above its expected congealing point, adjust the water bath to a temperature 7° to 8° below the expected congealing point. Stir the sample continuously during the remainder of the test by moving the loop up and down throughout the entire depth of the sample at a regular rate of 20 complete cycles per minute.

Record the reading of the test tube thermometer every 30 seconds. Continue stirring only so long as the temperature is gradually falling, stopping when the temperature becomes constant or starts to rise slightly. Pronounced supercooling may cause deviation from this normal pattern of temperature changes. If the latter occurs, repeat the test, introducing small particles of the material under test in solid form at 1° intervals as the temperature approaches the expected congealing point.

Continue recording the temperature in the test tube every 30 seconds for at least 3 minutes after the temperature again begins to fall after having remained constant. The average of not less than four consecutive readings that lie within a range of 0.2° constitutes the congealing point.

Congelation frequently may be induced by rubbing the inner walls of the test tube with the thermometer, or by introducing a small fragment of the previously congealed substance. Discontinue the stirring, and note the rise in temperature every 5 to 10 seconds. The highest temperature remaining constant for about 1 minute is the congealing temperature.

CONTAINERS—GLASS

Chemical Resistance

The following tests are designed to determine the resistance to water attack of new (not previously used) glass containers. The degree of attack is determined by the amount of alkali released from the glass under the influence of the attacking medium under the conditions specified. This quantity of alkali is extremely small in the case of the more resistant glasses, thus calling for particular attention to all details of the tests. All equipment used in these tests should be of high quality and precision and the tests should be conducted in an area relatively free from fumes and excessive dust.

Apparatus—*Autoclave*—For these tests use an autoclave capable of maintaining a temperature of 121 ± 0.5°, equipped with a thermometer, a pressure gauge, a vent cock, and a rack adequate to accommodate at least 12 test containers above the water level.

Mortar and Pestle—Use a hardened-steel mortar and pestle, made according to the specifications in the accompanying illustration.

Other Equipment—Also required are 20.3-cm. (8-inch) sieves including the No. 20, No. 40, and No. 50 sieves along with the pan and cover (see page 850), 250-ml. conical flasks made of resistant glass aged as specified, a 900-g. (2-lb.) hammer, a permanent magnet, a desiccator, and adequate volumetric apparatus.

Reagents—*Special Distilled Water*—The water used in these tests has a specific conductivity, determined at 20° just prior to use, of between 0.5 and 1 μmho. It meets the requirements of the *Heavy Metals Test*, page 806, and is free from copper. The water may be prepared by redistilling once-distilled water from a still of such proportions that the steam flows at low velocity when the still is operating at rated capacity. All parts of the still in contact with the water or steam are of borosilicate glass. Prior to distillation add, for each 1000 ml. of water contained in the still, 1 drop of phosphoric acid that previously has been diluted with an equal volume of distilled water and boiled to the point of appearance of dense fumes. Reject the first 10 or 15 percent of the distillate, and retain the next 75 percent.

Methyl Red Solution—Dissolve 24 mg. of sodium methyl red in sufficient purified water to make 100 ml. If necessary, neutralize the solution with 0.02 *N* sodium hydroxide so that the titration of 100 ml. of *Special Distilled Water*, containing 5 drops of indicator, does not require more than 0.02 ml. of 0.02 *N* sodium hydroxide to effect the color change of the indicator, which should occur at a pH of 5.6.

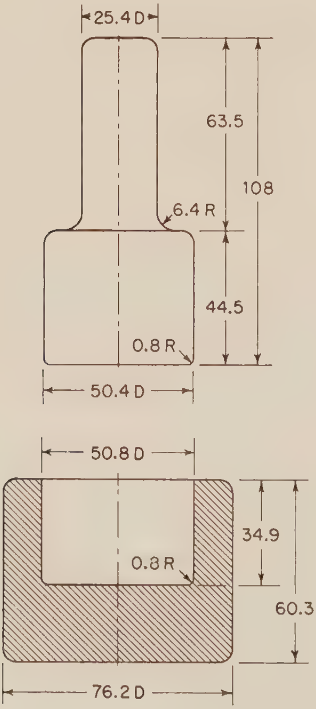
Powdered Glass Test—Rinse thoroughly with purified water six or more containers selected at random, and dry them with a stream of clean, dry air. Crush the containers into fragments about 25 mm. in size, divide about 100 g. of the coarsely

Glass Types and Test Limits

Type	General Description*	Type of Test	Limits	
			Size,† ml.	0.02 N Acid, ml.
I	Highly resistant, borosilicate glass	*Powdered Glass*	All	1.0
II	Treated soda-lime glass	*Water Attack*	100 or less	0.7
			Over 100	0.2
III	Soda-lime glass	*Powdered Glass*	All	8.5
NP	General-purpose soda-lime glass	*Powdered Glass*	All	15.0

* The description applied to containers of this type of glass usually available.
† Size indicates the overflow capacity of the container.

crushed glass into three approximately equal portions, and place one of the portions in the special mortar. With the pestle in place, crush the glass further by striking 3 or 4 blows with the hammer. Nest the sieves, and empty the mortar into the No. 20 sieve. Repeat the operation on each of the two remaining portions of glass, emptying the mortar each time into the No. 20 sieve. Shake the sieves for a short time, then remove the glass from the No. 20 and No. 40 sieves, and again crush and sieve as before. Repeat again this crushing and sieving operation. Empty the receiving pan, reassemble the nest of sieves, and shake on a mechanical sieve shaker for 5 minutes or by hand for an equivalent length of time. Transfer the portion retained on the No. 50 sieve, which should weigh in excess of 10 g., to a closed container, and store in a desiccator until used for the test.



Special Mortar and Pestle for Pulverizing Glass (Dimensions are in mm.)

Spread the sample on a piece of glazed paper, and pass a magnet through it to remove particles of iron that may be introduced during the crushing. Transfer the sample to a 250-ml. conical flask of resistant glass, and wash it with six 30-ml. portions of acetone, swirling each time for about 30 seconds and carefully decanting the acetone. After washing, the sample should be free from agglomerations of glass powder, and the surface of the grains should be practically free from adhering fine particles. Dry the flask and contents for 20 minutes at 140°, transfer the grains to a weighing bottle, and cool in a desiccator. Use the test sample within 48 hours after drying.

Procedure—Transfer 10.00 g. of the prepared sample to a 250-ml. conical flask that has been digested (aged) previously with *Special Distilled Water* in a bath at 90° for at least 24 hours or at 121° for 1 hour. Add 50.0 ml. of *Special Distilled Water* to this flask and to one similarly prepared to serve as a blank. Cap all flasks with chemically resistant, borosilicate glass beakers that have been digested in the same way as the flasks and are of such size that the bottoms of the beakers fit snugly down on the top rims of the containers. Place the containers in the autoclave, and close it securely, leaving the vent cock open. Heat until steam issues vigorously from the vent cock, and continue heating for 10 minutes. Close the vent cock, and adjust the temperature so that it rises 1° per minute until it reaches 121°, taking 19 to 23 minutes to reach the desired temperature. Hold the temperature at 121 ± 0.5° for 30 minutes, counting from the time when this temperature is reached. Reduce the heat so that the autoclave cools at the rate of 0.5° per minute and comes to atmospheric pressure in 38 to 46 minutes, being vented as needed to prevent the formation of a vacuum. Cool the flasks at once in running water, decant the water from the flasks into suitably cleaned vessels and wash the residual powdered glass with four 15-ml. portions of *Special Distilled Water*, adding the decanted washings to the main portion. Add 5 drops of *Methyl Red Solution*, and titrate immediately with 0.02 *N* sulfuric acid. If the volume of titrating solution is expected to be less than 10 ml., use a microburet. Record the volume of 0.02 *N* sulfuric acid used to neutralize the extract from 10 g. of the prepared sample of glass, corrected for a blank on the vessel in which the titration was carried out. The volume does not exceed that indicated in the accompanying table.

Water Attack at 121°—Rinse thoroughly 3 or more containers, selected at random, twice with *Special Distilled Water*.

Procedure—Fill each container to 90 percent of its overflow capacity with *Special Distilled Water*, and continue the test as directed for *Procedure* under *Powdered Glass Test*, beginning with "Cap all flasks," except that the time of autoclaving shall be 1 hour instead of 30 minutes, and ending with "to prevent the formation of a vacuum." Using a graduated cylinder, transfer 100 ml. of the water from each container or, in the case of smaller containers, the combined contents of several containers, into a 250-ml. conical flask of resistant glass, add 5 drops of *Methyl Red Solution*, and titrate, while warm, with 0.02 *N* sulfuric acid. Complete the titration within 60 minutes after opening the autoclave. Record the volume of 0.02 *N* sulfuric acid used, corrected for a blank obtained by titrating 100 ml. of *Special Distilled Water* at the same temperature and with the same amount of indicator.

Glass Types—Glass containers suitable for packaging official preparations may be classed as in the accompanying table on the basis of the foregoing tests. Types I, II, and III are intended for parenteral products. Type NP is intended for nonparenteral products, *i.e.*, those intended for oral or topical use.

Light Transmission

Apparatus—Use a spectrophotometer of suitable sensitivity and accuracy, adapted for measuring the amount of light transmitted by glass used for pharmaceutical containers.

Preparation of Sample—Cut the container in half lengthwise with a circular saw fitted with a wet abrasive wheel, such as a carborundum or a bonded diamond wheel. Trim a section of the side wall to obtain a segment of a size convenient for mounting in the spectrophotometer. After cutting, wash and dry the sample, taking care to avoid scratching the surfaces. If the sample is too small to cover the opening in the sample holder, mask the uncovered portion of the opening with opaque paper or masking tape, provided that the length of the sample is greater than that of the slit in the spectrophotometer. Immediately before mounting in the sample holder, wipe the sample with lens tissue. Mount the sample with the aid of a tacky wax, or by other convenient means, taking care to avoid leaving fingerprints or other marks on the surfaces through which light must pass.

Limits for Glass Types I, II, and III

Nominal Size in ml.	Maximum Percentage Light Transmission at Any Wavelength Between 290 mμ and 450 mμ	
	Flame-sealed Containers	Closure-sealed Containers
1	50	25
2	45	20
5	40	15
10	35	13
20	30	12
50	15	10

NOTE—Any container of a size intermediate to those listed above exhibits a transmission not greater than that of the next larger size container listed in the table. For containers larger than 50 ml., the limits for 50 ml. apply.

Blown glass containers vary substantially in their sidewall thickness, and limits in the above table and for type NP ware given elsewhere in this section apply to the average transmittance of the sidewalls.

Procedure—Place the sample in the spectrophotometer with its vertical axis parallel to the plane of the slit and approximately centered with respect to the slit. When properly placed, the light beam is normal to the surface of the sample and reflection losses are at a minimum.

Measure the transmittance of the sample with reference to air in the spectral region of 290 to 450 mμ, continuously with a recording instrument or at intervals of about 20 mμ with a manual instrument.

Limits—The observed light transmission does not exceed the limits given in the accompanying table for containers intended for parenteral use.

The observed light transmission for containers of Type NP glass does not exceed 10 percent at any wavelength in the range from 290 mμ to 450 mμ.

CONTENT UNIFORMITY

Capsules

Method I—Select a sample of 30 of the capsules to be tested, and assay 10 of these individually using the *Assay* procedure specified in the monograph. When the amount of drug in a single capsule is less than that required in the *Assay*, the degree of dilution of the solutions and/or the volume of aliquots should be adjusted so that the concentration of the drug in the final solution will be of the same order as that obtained in the *Assay* procedure; or, in the case of titrimetric assays, a more dilute titrant should be used, if necessary, so that an adequate volume of titrant will be required (see page 883). If any such modifications are made in the *Assay* procedure specified in the monograph, the appropriate corresponding changes must be made in the calculation formula, titration factor, etc., in order to obtain correct assay results.

The requirements are met if not less than 9 results fall within the limits of 85 percent to 115 percent of the mean of the tolerances specified in the rubric definition in the official monograph, and if all 10 results fall within the limits of 75 percent to 125 percent of the mean of the tolerances. If more than one result, but not more than three, falls outside the limits of 85 percent to 115 percent, assay the remaining 20 capsules individually. The requirements are met if all 30 results fall within the limits of 75 percent to 125 percent, and if not more than three results fall outside the limits of 85 percent to 115 percent.

Method II—Select a sample of 30 of the capsules to be tested, and assay 10 of these individually using the special procedure specified under *Content uniformity* in the monograph. Make any necessary correction of the results thus obtained as follows: (1) Remove and combine the contents of the number of capsules specified in the official *Assay* in the monograph, and assay an accurately weighed portion of the composite sample exactly as directed in the official *Assay*. (2) Assay another accurately weighed portion of the composite sample, equivalent to the gross weight of the contents of one capsule, using the special procedure specified under *Content uniformity* in the monograph. (3) Calculate (a) the weight of drug equivalent to one capsule using the results obtained by the official *Assay* procedure, and (b) the weight of drug equivalent to one capsule using the results obtained by the special procedure. (4) Calculate the correction factor, F, by the formula $F = P - A$, in which P is the weight of drug per capsule obtained by the special procedure, and A is the weight of drug per capsule obtained by the official *Assay* procedure. (5) Subtract the weight represented by F from each of the 10 assays performed on individual capsules by the special procedure.

The requirements are met if not less than 9 results thus corrected fall within the limits of 85 percent to 115 percent of the mean of the tolerances specified in the rubric definition in the official monograph, and if all 10 results fall within the limits of 75 percent to 125 percent of the mean of the tolerances. If more than one result, but not more than three, falls outside the limits of 85 percent to 115 percent, assay the remaining 20 capsules individually by the special procedure, and apply the correction factor as specified in steps (1) through (5) herein. The requirements are met if all 30 results fall within the limits of 75 percent to 125 percent, and if not more than three results fall outside the limits of 85 percent to 115 percent.

Sterile Solids

This test, when specified in the individual monograph, applies to sterile solids containing added substances (buffers, diluents, excipients, etc.). The test does not apply to sterile solids which contain no added substances or which are prepared from true solutions and are then subsequently dried in the final container. However, if the preparation has been lyophilized in the final container, the label must carry a statement to this effect in order for the preparation to be exempt from this content uniformity requirement; in addition, the preparation is required to meet the *Weight Variation Test for Sterile Solids*, page 902.

Method I—Select a sample of 30 of the containers to be tested, and assay the accurately weighed contents of 10 of these individually using the *Assay* procedure specified in the monograph. When the amount of drug in a single container is less than that required in the *Assay*, the degree of dilution of the solutions and/or the volume of aliquots should be adjusted so that the concentration of the drug in the final solution will be of the same order as that obtained in the *Assay* procedure; or in the case of titrimetric assays, a more dilute titrant should be used, if necessary, so that an adequate volume of titrant will be required (see page 883). If any such modifications are made in the *Assay* procedure specified in the monograph, the appropriate corresponding changes must be made in the calculation formula, titration factor, etc., in order to obtain correct assay results. The requirements are met if all 10 results fall within the limits of 85 percent to 115 percent of the mean of the tolerances specified in the rubric definition in the official monograph. If one, but not more than one, result falls outside these limits, assay the contents of the remaining 20 containers individually. The requirements are met if not more than one of the 30 results is outside the limits of 85 percent and 115 percent.

Method II—Select a sample of 30 of the containers to be tested, and assay the contents of 10 of these individually using the special procedure specified under *Content uniformity* in the monograph. Make any necessary correction of the results thus obtained as follows: (1) Prepare a composite sample by intimately mixing the contents of a sufficient number of containers to provide the amount of sample specified in the official *Assay* in the monograph plus the amount required for the special procedure specified under *Content uniformity* in the monograph. (2) Assay separate accurately weighed portions of the composite sample (a) exactly as directed in the official *Assay*, and (b) using the special procedure specified under *Content uniformity* in the monograph. (3) Calculate (a) the weight of drug equivalent to one container using the results obtained by the official *Assay* procedure, and (b) the weight of drug equivalent to one container using the results obtained by the special procedure. (4) Calculate the correction factor, F, by the formula $F = P - A$, in which P is the weight of drug per container obtained by the special procedure, and A is the weight of drug per container obtained by the official *Assay* procedure. (5) Subtract the weight represented by F from each of the 10 assays performed on individual containers by the special procedure.

The requirements are met if all 10 results thus corrected fall within the limits of 85 percent to 115 percent of the mean of the tolerances specified in the rubric definition in the official monograph. If one, but not more than one, result falls outside these limits, assay the contents of the remaining containers individually by the special procedure, and apply the correction factor as specified in steps 1 through 5 herein. The requirements are met if not more than one of the 30 results thus corrected is outside the limits of 85 percent to 115 percent.

Tablets

Method I—Select a sample of 30 of the tablets to be tested, and assay 10 of these individually using the *Assay* procedure specified in the monograph. When the amount of drug in a single tablet is less than that required in the *Assay*, the degree of dilution of the solutions and/or the volume of aliquots should be adjusted so that the concentration of the drug in the final solution will be of the same order as that obtained in the *Assay* procedure; or, in the case of titrimetric assays, a more dilute titrant should be used, if necessary, so that an adequate volume of titrant will be required (see page 883). If any such modifications are made in the *Assay* procedure specified in the monograph, the appropriate corresponding changes must be made in the calculation formula, titration factor, etc., in order to obtain correct assay results.

The requirements are met if all 10 results fall within the limits of 85 percent to 115 percent of the mean of the tolerances specified in the rubric definition in the official monograph. If one, but not more than one, result falls outside these limits, assay the remaining 20 tablets individually. The requirements are met if not more than one of the 30 results is outside the limits of 85 percent to 115 percent.

Method II—Select a sample of 30 of the tablets to be tested, and assay 10 of these individually using the special procedure specified under *Content uniformity* in the monograph. Make any necessary correction of the results thus obtained as follows: (1) Weigh and finely powder the number of tablets specified in the official *Assay* in the monograph, and assay an accurately weighed portion of the powder exactly as directed in the official *Assay*. (2) Assay another accurately weighed portion of the powder, equivalent to the gross weight of one tablet, using the special procedure specified under *Content uniformity* in the monograph. (3) Calculate (a) the weight of drug equivalent to one tablet using the results obtained by the official *Assay* procedure, and (b) the weight of drug equivalent to one tablet using the results obtained by the special procedure. (4) Calculate the correction factor, F, by the formula $F = P - A$, in which P is the weight of drug per tablet obtained by the special procedure, and A is the weight of drug per tablet obtained by the official *Assay* procedure. (5) Subtract the weight represented by F from each of the 10 assays performed on individual tablets by the special procedure.

The requirements are met if all 10 results thus corrected fall within the limits of 85 percent to 115 percent of the mean of the tolerances specified in the rubric definition in the official monograph. If one, but not more than one, result falls outside these limits, assay the remaining 20 tablets individually by the special procedure, and apply the correction factor as specified in steps (1) through (5) herein. The requirements are met if not more than one of the 30 results thus corrected is outside the limits of 85 percent to 115 percent.

COULOMETRY

Coulometry is an electrochemical method of analysis related to polarography (see page 847) and based on Faraday's law. It requires the accurate measurement of the quantity of electricity passed at the electrodes during an electron transfer involving a chemical change. The quantity of electricity can be expressed as

$$Q = \int_0^t i dt.$$

Various methods are used to evaluate Q.

Coulometric analyses may be conducted either under conditions in which the current flowing through the cell is maintained constant (constant current coulometry), or under conditions in which the potential at the working electrode is maintained constant (constant potential coulometry). The discussion which follows relates to the latter.

Potential Control—Constant potential coulometry requires the electrode reaction to occur with 100 percent current efficiency, and that there be no secondary electrode reactions. To accomplish this, the working electrode is maintained at a potential which permits the quantitative reaction of the electroactive substance. If a reversible reaction is involved, the electrode potential (E) can be determined from the Nernst equation, at 25°, by the formula

$$E = E^0_{25°} + \frac{0.059}{n} \log \frac{[\mathrm{Ox}]}{[\mathrm{Red}]},$$

in which E^0 is the formal potential, which is equivalent to E when the oxidized and reduced forms are at unit concentrations: and n is the number of electrons transferred. The potential is calculated for a ratio of oxidized to reduced form of 1/1000 when the reaction is reduction. A more practical approach is to determine the potential from the limiting current plateau of a polarographic current-voltage curve using similar electrodes. The polarographic potentials will be applicable to coulometry if the cell resistance is low (or compensated for). The most reliable method is to determine the amount of the sample reacted in the coulometric cell by increasing the potential in about 50-mv. intervals and plotting the percent reacted *versus* the applied potential. The plot obtained has the form of a current-voltage curve and a potential can be chosen for which there is a 100 percent reaction.

The selected potential is maintained by a potentiostat which compensates for changes in the iR drop (the potential needed to pass the current, i, through the solution with a resistance, R) due to depletion of the electroactive species from the sample solution. In general, for reductions, a stoichiometric reaction is more easily attainable with the mercury pool electrode than with platinum or other solid electrodes. When controlled potential conditions are maintained, the current decreases exponentially in a manner analogous to the radioactive-decay law,

$$i_t = i_o e^{-k(t)}, \text{ or } k = \frac{2.303}{t} \log \frac{i_o}{i_t},$$

in which i_o is the initial current, i_t is the cell current at time t, and k is a function of the electrode surface area, the stirring rate, the volume of solution, the temperature, and the nature of the electrode reaction. The constant k can be evaluated by determining the current at any two times, as long as the stirring rate and mass transfer rate are not altered during the reaction. A k value greater than 0.1 indicates that the reaction is proceeding rapidly.

Electrolysis Cell—Several types of cell arrangements can be employed when specific reactions are under investigation. Generally, the cell has about a 50- to 100-ml. capacity and also has provisions for making electrical contact between the potentiostat and the mercury pool. Also required are a nitrogen gas (pre-conditioned) bubbling tube and a means of stirring the mercury pool-sample solution interface (usually by a motor-driven glass propeller or other suitable stirring device). The working, reference, and counter electrodes are in isolated compartments.

Controlled Working Electrode—The mercury pool is commonly used for reduction reactions and oxidation reactions in which the potential required does not cause anodic decomposition of the mercury electrode. This is usually not greater than 0.0 volts *versus* the saturated calomel reference electrode, but is dependent upon the nature of the electrolyte. A platinum screen is used for reactions which are more anodic than about 0.0 volts.

Reference Electrode—A calomel or silver/silver chloride electrode which has a large surface area and low resistance is routinely used.

Counter Electrode—This is usually a

platinum electrode and must be separated from the sample solution by a fritted-glass disk to prevent the gases formed at the electrode from reacting with the sample solution or the product of the reaction at the controlled working electrode. With truly reversible reductions, the reduction product will be reoxidized at the counter electrode, thereby destroying stoichiometry, if the counter electrode is not isolated from the working electrode.

Coulometers and *Q* Determination—The extent of the electrochemical reaction in terms of the coulombs of electricity which flow can be determined by mathematical integration of the current-time equation. Inaccuracies may occur when a mercury pool is used, because the mass transfer rate changes due to the inconsistent surface area of the stirred mercury pool. For more accurate determinations, a coulometer in series with the electrolysis cell provides an adequate measurement.

Several types of chemical coulometers are commonly employed. The silver coulometer involves electrolysis of a silver nitrate solution at a tared platinum cathode. The amount of silver deposited onto the electrode surface is determined by reweighing. From the electrochemical equivalent of silver, the coulombs of electricity are calculated. In a gas coulometer, the volume of the gas formed at the platinum anode and/or cathode (oxygen and/or hydrogen) is proportional to the coulombs of electricity which flow through the cell. The volume can be measured accurately by means of a gas buret. The amount of iodine or iodide which reacts at the platinum cathode or anode in the iodine coulometer is proportional to the number of coulombs of electricity and can be determined by volumetric titration of the iodine formed, or by back titration of the unconsumed iodine.

The most rapid method of measuring the number of coulombs transferred is by electronic integration of a current-time curve. This approach is as accurate as any of the chemical methods and has the advantage that the number of coulombs is determined as soon as the reaction is completed, without additional manipulations.

End-Point Determination—When the current has decayed to at least 1/1000 of the initially observed current, the reaction is considered quantitative. Sometimes the current does not decrease to the desired level, but to a background current which can be composed of a charging current and/or a faradaic current due to impurities in the system. A blank determination will correct for these extraneous currents.

Calculation—A coulomb is the quantity of electricity passed when one ampere of current flows for one second. The reaction of one gram equivalent weight, at an electrode, involves the passage of 96,493 coulombs of electricity, or one Faraday (F). The electrochemical equivalent is the weight, in g., which reacts due to the flow of one coulomb of electricity. From the number of coulombs (Q), the quantity (W, in g.) of electroactive substance may be calculated. This relationship may be expressed as

$$W = \frac{QM}{n\ 96{,}493},$$

in which M represents the molecular weight of the substance, and n represents the number of electrons involved in the process.

Procedure—(*Caution:* Mercury is poisonous. Work in a well-ventilated laboratory taking care to clean up any spilled mercury.) Transfer the sample to the cell, and dissolve it in the supporting electrolyte, if it is not already in solution. Position the electrodes in place, and deaerate with scrubbed nitrogen for 10 to 15 minutes to remove any dissolved oxygen. Stir the solution and the mercury pool so that the mercury does not splatter. Control the temperature as stated in the individual monograph, if necessary, and electrolyze the sample at the potential indicated in the individual monograph. Determine the coulombs of electricity passed, using a suitable coulometer and correcting for a blank determination similarly performed. Calculate the weight, in g., of active electrolyzable sample from the electrochemical equivalent indicated in the individual monograph.

DEPRESSOR SUBSTANCES TEST

Anesthetize an adult cat by intraperitoneal injection of an anesthetic substance, such as sodium phenobarbital, that is favorable to maintenance of uniform blood pressure. Immobilize the animal, and cover it to prevent excessive loss of body heat during the test. If preferable, or necessary, insert a tracheal cannula so that the animal may receive artificial respiration. By surgical means expose a carotid artery and insert a cannula connected to a manometer arranged for making a continuous record of the blood pressure. Expose a femoral vein to facilitate intravenous injection.

Determine the sensitivity of the animal to histamine by injecting, at uniform time intervals of not less than 5 minutes, doses of a solution of USP Histamine Dihydrochloride Reference Standard containing the equivalent of 1.0 mcg. of histamine base per ml. Inject doses corresponding to

0.05, 0.1, and 0.15 mcg. of histamine base per kg. of body weight of the animal. Determine the extent of variation in depressor response to the same dose by repeating the injection of 0.1 mcg. per kg. Use the animal for the test only if the responses to several injections of this dose are approximately the same and correspond to a decrease in pressure of not less than 20 mm. of mercury.

Dissolve the substance under test in sufficient saline T.S. to give the concentration specified in the individual monograph. Following the same time schedule established during the injection of the standard histamine solution, inject a series of four doses consisting of the solution under test in the dosage specified in the individual monograph, alternated with a dose of the standard solution equivalent to 0.1 mcg. of histamine base per kg. Measure the change in blood pressure following each of the four injections. The average depressor response to the solution under test is not greater than that obtained with the dose representing 0.1 mcg. per kg. of histamine base.

DISSOLUTION TEST

This test is designed to determine compliance with the limits on *Dissolution* when stated in the individual monograph for a tablet or capsule dosage form. Use either *Method I* or *Method II* as directed in the individual monograph.

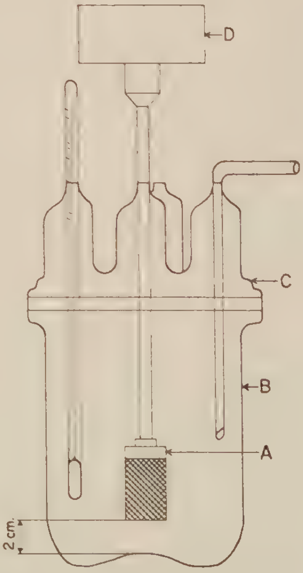
This *in vitro* method *per se* is not designed to assure or measure the safety or effectiveness of the article being tested. Both safety and effectiveness of a specific formulation must be initially demonstrated through appropriate *in vivo* studies and clinical evaluation. In itself, this test does provide an objective means of determining the dissolution characteristics of a solid dosage form, although it is recognized that by correlating *in vivo* test data and clinical evaluation, more precise *in vitro* dissolution limits might subsequently be established. Since drug absorption and physiological availability often are largely dependent upon the drug being in the dissolved state, suitable dissolution characteristics can be an important property of a satisfactory drug product. On this basis, specific test conditions and dissolution limits are provided in certain NF tablet or capsule monographs.

Method I

Apparatus—Unless otherwise specified the apparatus, as shown in the accompanying diagram, consists of: a rotating-basket assembly* (A), fabricated from Type 316 stainless steel throughout; a suitable vessel (B) (preferably a 1000-ml. resin flask†) to contain the dissolution fluid; a four-hole cover for the vessel (C); and a high-torque stirring motor (D) equipped with a speed-regulating device capable of rotation at specified speeds, ±5%, varying from 25 r.p.m. to 200 r.p.m. The assembly is immersed in a constant-temperature bath maintained at 37 ± 0.5°. The rotating basket is a cylinder 3.6 cm. in height and 2.5 cm. in diameter, the sides and bottom of which are 40-mesh stainless steel cloth. The cylinder is joined at the seam by welding and is welded at the top and bottom to stainless steel rings. A 6-mm. × 30-cm. stainless steel rod, attached to a 2.5-cm. plate having a 2-mm. vent and three spring clips, is used to hold the basket. The stirring rod of the rotating basket assembly is placed through the center hole of the vessel cover and is centered by suitable means to permit smooth rotation and to prevent wobbling. A thermometer is inserted in the second hole, and the remaining two holes are used for sampling and exchange of fluids.

Dissolution Fluid—Use the medium specified in the individual monograph.

Procedure—Unless otherwise directed, place 900 ml. of the *Dissolution Fluid* in



Apparatus for Dissolution Test, Method

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* Available from Hanson Research Corporation, 10945 Nestle Avenue, Northridge, CA 91324.

† Such as Kimble #33700, or Pyrex No. 6947.

the vessel, immerse in the constant temperature bath, and allow the *Dissolution Fluid* to come to 37 ± 0.5°. Place one tablet or capsule in the basket, assemble the apparatus, and immerse the basket to a point 2.0 ± 0.2 cm. from the bottom of the vessel. Begin stirring at the rate specified in the individual monograph, and continue as directed in the individual monograph. Repeat the test on five additional dosage units: all six dosage units (tablets or capsules) dissolve as stated in the test requirements in the individual monograph. If 1 or 2 dosage units fail to dissolve as stated, repeat the test on six additional dosage units: not less than 10 of the 12 dosage units dissolve as stated. [Note: Unless otherwise specified, maintain the volume in the vessel constant by adding a volume of *Dissolution Fluid* equivalent to that removed for sampling purposes.]

Method II

Apparatus—Use an *Apparatus* and a *Basket-rack Assembly* as described under *Tablet Disintegration Test*, page 878, except (*a*) replace the 10-mesh stainless steel cloth in the *Basket-rack Assembly* with a 40-mesh stainless steel cloth (of Type 316) [Note—A 40-mesh stainless steel cloth should be affixed to the top of the *Basket-rack Assembly*, if necessary, to provide for immersion in the *Dissolution Fluid* of tablets or capsules which otherwise would float on the surface of the *Fluid*.]; and (*b*) adjust the *Apparatus* so that it descends to 1 ± 0.1 cm. from the bottom of the vessel on the downward stroke. [Note—The *Disks* (see page 878) are not used in this test.]

Dissolution Fluid—Use the medium specified in the individual monograph.

Procedure—Proceed as directed in the individual monograph.

EPINEPHRINE ASSAY

Ferro-citrate Solution—On the day needed, dissolve 1.5 g. of ferrous sulfate in 200 ml. of water to which have been added 1.0 ml. of 1 *N* hydrochloric acid and 1.0 g. of sodium bisulfite, and dissolve 500 mg. of sodium citrate in 10 ml. of this solution.

Buffer Solution—Add 42 g. of sodium bicarbonate and 50 g. of potassium bicarbonate to about 180 ml. of water. (Not all of the solids will dissolve at this stage.) To another 180 ml. of water add 37.5 g. of aminoacetic acid and 17 ml. of stronger ammonia water. Mix the two solutions, add water to make 500 ml., and mix until solution is complete.

Standard Preparation—Transfer about 18.2 mg. of USP Epinephrine Bitartrate Reference Standard, previously dried in a vacuum desiccator over silica gel for 18 hours and accurately weighed, to a 100-ml. volumetric flask with the aid of 20 ml. of sodium bisulfite solution (1 in 50), add water to volume, and mix. Pipet 1.0 ml. of this solution into a 10-ml. graduated cylinder or flask, add sodium bisulfite solution (1 in 500) to make 10.0 ml., and mix. [Note: Make the final dilution when the assay is carried out.]

Assay Preparation—Pipet into a 10-ml. graduated cylinder or flask a volume of the Injection under assay, equivalent to about 100 mcg. of epinephrine, add sodium bisulfite solution (1 in 500) to make 10.0 ml., and mix.

Procedure—To each of the vessels containing the *Assay Preparation* and the *Standard Preparation*, add 0.1 ml. of *Ferro-citrate Solution* and 1.0 ml. of *Buffer Solution*, and mix. Allow to stand for 30 minutes, then determine the absorbance of each solution in 1-cm. cells, at 530 mμ, with a suitable spectrophotometer, using water as the blank. Record the absorbance of the solution from the *Standard Preparation* as A_S and that from the *Assay Preparation* as A_U. Calculate the quantity, in mg., of epinephrine ($C_9H_{13}NO_3$) in each ml. of the Injection taken by the formula $0.01 \times (C/V) \times (0.5497\ A_U/A_S)$, in which C is the exact quantity, in mcg., of USP Epinephrine Bitartrate Reference Standard per ml. of the *Standard Preparation*, V is the volume, in ml., of the Injection taken, and 0.5497 is the factor converting epinephrine bitartrate to epinephrine.

FATS AND FIXED OILS

The following definitions and general procedures apply to fats, fixed oils, waxes, resins, balsams, and similar substances.

Preparation of Sample

If a sample of oil shows turbidity owing to separated stearin, warm the container in a water bath at 50° until the oil is clear, or if the oil does not become clear on warming, filter it through dry filter paper in a funnel contained in a hot water jacket. Thoroughly mix, and weigh at one time as many portions as are needed for the various determinations, using preferably a bottle having a pipet dropper or weighing buret. Keep the sample melted, if solid at room temperature, until the desired samples are withdrawn.

Specific Gravity

Determine the specific gravity of a fat or oil as directed under *Specific Gravity*, page 866.

Melting Temperature

Determine the melting temperature as directed for substances of *Class II* (see page 815).

Solidification Temperature of Fatty Acids

(Frequently referred to as the "titer.")

Preparation of the Fatty Acids—Heat 75 ml. of glycerin-potassium hydroxide solution (made by dissolving 25 g. of potassium hydroxide in 100 ml. of glycerin) to 150° in an 800-ml. beaker, and add 50 ml. of the clarified fat, melted if necessary. Heat the mixture for 15 minutes with frequent stirring, but do not allow the temperature to rise above 150°. Saponification is complete when the mixture is homogeneous, with no particles clinging to the beaker at the meniscus. Pour the contents of the beaker into 500 ml. of nearly boiling water in an 800-ml. beaker or casserole, add slowly 50 ml. of dilute sulfuric acid (made by adding 1 volume of sulfuric acid to 3 volumes of water), and heat the solution, with frequent stirring, until the fatty acids separate cleanly as a transparent layer. Wash the acids with boiling water until free from sulfuric acid, collect them in a small beaker, place on a steam bath until the water has settled and the fatty acids are clear, filter into a dry beaker while hot, and dry for 20 minutes at 105°.

Test for Complete Saponification—Place 3 ml. of the dry acids in a test tube and add 15 ml. of alcohol. Heat the solution to boiling, and add an equal volume of ammonia T.S. A clear solution results.

Procedure—Using an apparatus similar to the "Congealing Temperature Apparatus" specified therein, proceed as directed for the first four paragraphs of *Procedure* under *Congealing Range or Temperature*, page 794, reading "solidification temperature" for "congealing point." The average of not less than four consecutive readings of the highest point to which the temperature rises is the solidification temperature of the fatty acids.

Acid Value (Free Fatty Acids)

The acidity of fats and fixed oils may be expressed in this NF as the number of ml. of 0.1 *N* alkali required to neutralize the free acids in 10 g. of substance. Acidity is frequently expressed as the Acid Value, which is the number of mg. of potassium hydroxide required to neutralize the free acids in 1 g. of the substance.

Procedure—Unless otherwise directed, dissolve about 10 g. of the substance, accurately weighed, in 50 ml. of a mixture of equal volumes of alcohol and ether (which has been neutralized to phenolphthalein with 0.1 *N* sodium hydroxide) contained in a flask. If the sample does not dissolve in the cold solvent, connect the flask with a reflux condenser and warm slowly, with frequent shaking, until the sample dissolves. Add 1 ml. of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide until the solution remains faintly pink after shaking for 30 seconds. Calculate either the Acid Value or the volume of 0.1 *N* alkali required to neutralize exactly 10 g. of sample, whichever is appropriate.

If the oil has been saturated with carbon dioxide for the purpose of preservation, gently reflux the alcohol-ether solution for 10 minutes before titration. The oil may be freed from carbon dioxide also by exposing it in a shallow dish in a vacuum desiccator for 24 hours before weighing the samples.

Ester Value

The Ester Value is the number of mg. of potassium hydroxide required to saponify the esters in 1 g. of the substance. If the *Saponification Value* and the *Acid Value* have been determined, the difference between these two represents the Ester Value.

Procedure—Place 1.5 to 2 g. of the substance in a 250-ml. tared flask, weigh accurately, add 20 to 30 ml. of neutralized alcohol, and shake. Add 1 ml. of phenolphthalein T.S., and titrate with 0.5 *N* alcoholic potassium hydroxide until the free acid is neutralized. Add 25.0 ml. of 0.5 *N* alcoholic potassium hydroxide, and proceed as directed under *Saponification Value*, page 805, beginning with "Insert into the neck of the flask" and omitting the further addition of phenolphthalein T.S. The volume, in ml., of 0.5 *N* hydrochloric acid consumed, corrected for the blank, multiplied by 28.05 and divided by the weight in g. of the sample taken, is the Ester Value.

Iodine Value (Hanus Method)

The Iodine Value represents the number of g. of iodine absorbed, under the prescribed conditions, by 100 g. of the substance.

Procedure—Introduce about 800 mg. of a solid fat or about 200 mg. of an oil, accurately weighed, into a 250-ml. iodine flask, dissolve it in 10 ml. of chloroform, add 25.0 ml. of iodobromide T.S., stopper the vessel securely, and allow it to stand for 30 minutes protected from light. Then add, in the order named, 30 ml. of potassium iodide T.S. and 100 ml. of water, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, shaking thoroughly after each addition of thiosulfate. When the iodine color becomes quite pale, add 1 ml. of starch T.S. and continue the titration with 0.1 N sodium thiosulfate until the blue color is discharged. Carry out a blank test at the same time with the same quantities of the same reagents and in the same manner (see *Residual Titrations*, page 883). The difference between the volumes, in ml., of 0.1 N sodium thiosulfate consumed in the blank test and the actual test, multiplied by 1.269 and divided by the weight in g. of the sample taken, is the Iodine Value.

NOTE: If more than half of the iodobromide T.S. reacts with the portion of the substance taken, repeat the determination, using a smaller portion of the substance under examination.

Saponification Value

The Saponification Value is the number of mg. of potassium hydroxide required to neutralize the free acids and saponify the esters contained in 1 g. of the substance.

Procedure—Place 1.5 to 2 g. of the substance in a tared, 250-ml. flask, weigh accurately, and add to it 25.0 ml. of 0.5 N alcoholic potassium hydroxide. Insert into the neck of the flask, by means of a perforated stopper, an air condenser consisting of a glass tube 70 to 80 cm. in length and 5 to 8 mm. in diameter, and heat the flask on a steam bath for 30 minutes, frequently rotating the contents. Then add 1 ml. of phenolphthalein T.S., and titrate the excess potassium hydroxide with 0.5 N hydrochloric acid. Run a blank test at the same time, using the same amount of 0.5 N alcoholic potassium hydroxide (see *Residual Titrations*, page 883). The difference between the volumes, in ml., of 0.5 N hydrochloric acid consumed in the actual test and in the blank test, multiplied by 28.05 and divided by the weight in g. of sample taken, is the Saponification Value.

If the oil has been saturated with carbon dioxide for the purpose of preservation, expose it in a shallow dish in a vacuum desiccator for 24 hours before weighing the samples.

Unsaponifiable Matter

The term, Unsaponifiable Matter, in oils or fats, refers to those substances that are not saponifiable by alkali hydroxides but are soluble in the ordinary fat solvents, and to products of saponification that are soluble in such solvents.

Procedure—Weigh 5.0 g. of the oil or fat into a 250-ml. conical flask, add a solution of 2 g. of potassium hydroxide in 40 ml. of alcohol, and heat under a reflux condenser for 2 hours, keeping the alcohol gently boiling. Evaporate the alcohol on a steam bath, dissolve the residue in 50 ml. of hot water, and transfer the solution to a separator, rinsing the flask with two 25-ml. portions of hot water which are added to the separator (do not use grease on stopcock). Cool to room temperature, add a few drops of alcohol to facilitate the separation of the two liquids, and extract with two successive 50-ml. portions of ether, combining the ether extracts in another separator. Wash the combined extracts first with 20 ml. of sodium hydroxide solution (4 in 1000), then with 20 ml. of sodium hydroxide solution (8 in 1000), and finally with 15-ml. portions of water until the last washing is not reddened by the addition of 2 drops of phenolphthalein T.S. Transfer the ether extract to a tared beaker, and rinse the separator with 10 ml. of ether, adding the rinsings to the beaker. Evaporate the ether on a steam bath just to dryness, and dry the residue for 30 minutes at 100°. Cool the beaker in a desiccator for 30 minutes, and weigh the residue of Unsaponifiable Matter.

Water and Sediment in Fixed Oils

Apparatus—The preferred centrifuge has a diameter of swing (d = distance from tip to tip of whirling tubes) of 38 to 43 cm. and is operated at a speed of about 1500 r.p.m. If a centrifuge of different dimensions is used, calculate the desired rate of revolution by the formula, r.p.m. = $1500\sqrt{40.6/d}$.

The centrifuge tubes are pear-shaped, and are shaped to accept closures. The total capacity of each tube is about 125 ml. The graduations are clear and distinct, reading upward from the bottom of the tube according to the following scale:

Volume	Scale Division
0 to 3 ml.	0.1 ml.
3 to 5 ml.	0.5 ml.
5 to 10 ml.	1.0 ml.
10 to 25 ml.	5.0 ml.
25 to 50 ml.	25.0 ml.
50 to 100 ml.	50.0 ml.

Procedure—Place 50.0 ml. of benzene in each of two centrifuge tubes and to each tube add 50.0 ml. of the oil, warmed if necessary to re-incorporate separated stearin, and thoroughly mixed, at 25°. Tightly stopper the tubes and shake them vigorously until the contents are thoroughly mixed, then immerse the tubes in a water bath at 50° for 10 minutes. Centrifuge for 10 minutes. Read the combined volume of water and sediment at the bottom of each tube. Centrifuge repeatedly for 10-minute periods until the combined volume of water and sediment remains constant for 3 consecutive readings. The sum of the volumes of combined water and sediment in the two tubes represents the percentage, by volume, of water and sediment in the oil.

HEAVY METALS TEST

This test is provided to demonstrate that the content of metallic impurities that are colored by hydrogen sulfide, under the specified conditions, does not exceed the *Heavy metals* limit given in the individual monograph in terms of the parts (by weight) of lead per million parts of the test substance, as revealed by a parallel comparison with a standard lead solution.

Method I is for the simpler and colorless substances, while Method II is for colored substances and those which by virtue of their complex nature interfere with the precipitation of heavy metals by sulfide.

Special Reagents

Ammonia T.S.—The heavy metals limit of the ammonia T.S. used in this test is 2 parts per million, when determined as directed under *Strong Ammonia Solution*, page 41.

Hydrochloric Acid—Prepare all solutions of hydrochloric acid used in the Heavy Metals Test from reagent hydrochloric acid (see USP XVIII).

Lead Nitrate Stock Solution—Dissolve 159.8 mg. of lead nitrate in 100 ml. of water to which has been added 1 ml. of nitric acid, then dilute with water to 1000 ml. Prepare and store this solution in glass containers free from soluble lead salts.

Standard Lead Solution—Dilute 10.0 ml. of *Lead Nitrate Stock Solution* with water to 100.0 ml. This solution must be freshly prepared. Each ml. of *Standard Lead Solution* contains the equivalent of 10 mcg. of lead. A comparison solution prepared on the basis of 0.1 ml. of *Standard Lead Solution* per g. of substance being tested contains the equivalent of 1 part of lead per million parts of the substance tested.

Procedure for Chemicals

Method I—*Solution A*—Pipet into a 50-ml. color-comparison tube a volume of *Standard Lead Solution* containing the lead equivalent of the heavy metals limit specified for the substance to be tested. Calculate the volume, in ml., of *Standard Lead Solution* required by the formula $0.1W \times L$, in which W is the weight, in g., of the sample in the final volume of solution prepared for the test as directed in an individual monograph, and L is the *Heavy metals* limit, in parts per million. Add water to make 25 ml., adjust the pH to between 3 and 4 (short-range pH indicator paper) by addition of diluted acetic acid or ammonia T.S., dilute with water to 40 ml., and mix.

Solution B—Place in a 50-ml color-comparison tube that matches the one used for Solution A, 25 ml. of the solution prepared for the test as directed in the individual monograph, adjust the pH to between 3 and 4 (short-range pH indicator paper) by addition of diluted acetic acid or ammonia T.S., dilute with water to 40 ml., and mix.

Procedure—Add 10 ml. of freshly prepared hydrogen sulfide T.S. to each tube, mix, allow to stand for 5 minutes, and view downward over a white surface: the color of Solution B is no darker than that of Solution A.

Method II—Use 1.0 g. of the substance for this test, unless the heavy metals limit is more than 30 parts per million, in which case use 500 mg. Proceed as directed under *Method I*, but use the following in place of *Solution B*.

Place the weighed quantity of the substance in a suitable crucible, and carefully ignite at a low temperature until thoroughly charred. The crucible may be loosely covered with a porcelain lid during the charring. Add to the contents of the crucible 2 ml. of nitric acid and 5 drops of sulfuric acid, and cautiously heat until white fumes are evolved, then ignite, preferably in a muffle furnace, at 500° to 600° until the carbon is all burned off. Cool, add 2 ml. of hydrochloric acid, and slowly evaporate on a steam bath to dryness. Moisten the residue with 1 drop of hydrochloric acid, add 10 ml. of hot water, and digest for 2 minutes. Add, dropwise, ammonia T.S. until the solution is just alkaline to litmus paper, dilute with water to 25 ml., and adjust the pH to between 3 and 4 (short-range pH indicator paper) by addition of diluted acetic acid. Filter if necessary, wash the crucible and the filter with 10 ml. of water, dilute the combined filtrate and washings with water to 40 ml., and mix.

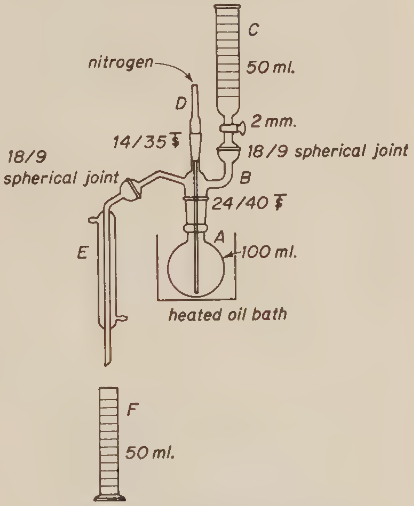
Procedure for Volatile Oils

Shake 10 ml. of the oil with an equal volume of water to which 1 drop of hydrochloric acid has been added, and pass hydrogen sulfide through the mixture until it is saturated: no darkening in color is produced in either the oil or the water.

HYDROXYPROPOXY DETERMINATION

Apparatus—The apparatus for hydroxypropoxy group determinations is shown diagrammatically in the accompanying figure. The boiling flask, *A*, is fitted with a distilling head, *B*. The distilling head is fitted with a gas delivery tube, *D*, for the introduction of nitrogen, a 50-ml. graduated dropping funnel, *C*, for the introduction of water, and a condenser, *E*. The distillate is collected in a 50-ml. graduate, *F*. The boiling flask is immersed in an oil bath equipped with a thermoregulator so that the oil can be maintained at a temperature of 155°.

Procedure—Transfer about 50 mg. of Hydroxypropyl Methylcellulose, previously dried at 105° for 2 hours, into flask *A* and add 10 ml. of chromium trioxide solution (60 g. in 140 ml.). Immerse the flask in the oil bath to two-thirds of its height, assemble the apparatus, and pass nitrogen gas through it at the rate of one and one-half bubbles per second. Raise the temperature of the oil bath to 155° during a 30-minute period and maintain it at this temperature until the end of the determination. Distillation begins between 135° and 140°, and as successive 5-ml. volumes of distillate collect in the 50-ml. graduate, add 5-ml. portions of distilled water to the flask from the 50-ml. graduated dropping funnel. Continue this procedure until 50 ml. of water has been added and 55 ml. of distillate, which should be faintly yellow in color, has been collected. Detach the condenser from the still head and wash it with water, collecting the washings in a 250-ml. conical flask. Transfer the contents of the 50-ml. graduate to the flask containing the washings. Add a few drops of phenolphthalein T.S., and titrate the combined solution with 0.02 N sodium hydroxide until the end-point just begins to fade. Heat the solution nearly to the boiling point to remove carbon dioxide, cool to room temperature, and continue the titration until the pink color remains stable for 10 seconds. Record the volume (x) of the 0.02 N sodium hydroxide used, and then add 500 mg. of sodium bicarbonate and 10 ml. of diluted sulfuric acid. After evolution of carbon dioxide has ceased, add 1 g. of potassium iodide, stopper the flask, shake the mixture, and allow the solution to stand in the dark for 5 minutes. Titrate the liberated iodine with 0.02 N sodium thiosulfate to the sharp disappearance of the yellow iodine color, adding a few drops of starch T.S. to confirm the end-point, and record the volume (y) required. Correct the volume (x) of 0.02 N sodium hydroxide required for the initial titration, in order to obtain the equivalent of acetic acid, by the formula $x - Ky$, in which K represents the ratio (ml. 0.02 N sodium hydroxide from the blank)/(ml. 0.02 N sodium thiosulfate from the blank), obtained by performing a blank determination with the same quantities of the same reagents and in the same manner. Each ml. of the corrected volume of 0.02 N sodium hydroxide is equivalent to 1.5 mg. of hydroxypropoxy groups ($—OCH_2CHOHCH_3$).



Apparatus for Hydroxypropoxy Group Determination

IDENTIFICATION—GENERAL TESTS

Under this heading are placed tests which are frequently referred to in the National Formulary for the identification of official articles.

The tests are not intended to be applicable to mixtures of substances unless so specified.

Acetate—When acetic acid or an acetate is warmed with sulfuric acid and alcohol, ethyl acetate, recognizable by its characteristic odor, is evolved. With neutral solutions of acetates, ferric chloride T.S. produces a deep red color which is destroyed by the addition of mineral acids.

Aluminum—Solutions of aluminum salts yield with ammonia T.S. a gelatinous, white precipitate which is insoluble in an excess of ammonia T.S. Sodium hydroxide T.S. or sodium sulfide T.S. produces the same precipitate which dissolves in an excess of either of these reagents.

Ammonium—Ammonium salts are decomposed by the addition of an excess of sodium hydroxide T.S., with the evolution of ammonia, recognizable by its odor and by its alkaline effect upon moistened red litmus paper exposed to the vapor. Warming the solution accelerates the decomposition.

Antimony—Solutions of antimonous compounds, strongly acidified with hydrochloric acid, yield with hydrogen sulfide an orange precipitate of antimony sulfide which is insoluble in ammonia T.S., but soluble in ammonium sulfide T.S.

Barium—Solutions of barium salts yield a white precipitate with diluted sulfuric acid. This precipitate is insoluble in hydrochloric and in nitric acid. Barium salts impart a yellowish green color to a nonluminous flame, which appears blue when viewed through green glass.

Benzoate—In neutral solutions, benzoates yield a salmon-colored precipitate with ferric chloride T.S. In moderately concentrated solutions, benzoates yield a precipitate of benzoic acid upon acidification with diluted sulfuric acid. This precipitate is readily soluble in ether.

Bicarbonate—See *Carbonate.*

Bismuth—When dissolved in a slight excess of nitric or hydrochloric acid, bismuth salts yield a white precipitate upon dilution with water. This precipitate is colored brown by hydrogen sulfide, and the resulting compound dissolves in a warm mixture of equal parts of nitric acid and water.

Bisulfite—See *Sulfite.*

Borate—To 1 ml. of a borate solution, acidified to litmus with hydrochloric acid, add 3 or 4 drops of iodine solution (1 in 1000) and 3 or 4 drops of polyvinyl alcohol solution (1 in 50): an intense blue color is produced. When a borate is treated with sulfuric acid, methanol added, and the mixture ignited, it burns with a green-bordered flame.

Bromide—Solutions of bromides, upon the addition of chlorine T.S., dropwise, liberate bromine, which is dissolved by shaking with chloroform, coloring the chloroform red to reddish brown. Silver nitrate T.S. produces in solutions of bromides a yellowish white precipitate, which is insoluble in nitric acid and slightly soluble in ammonia T.S.

Calcium—Solutions of calcium salts form insoluble oxalates when treated as follows: To a solution of the calcium salt (1 in 20) add 2 drops of methyl red T.S., and neutralize with ammonia T.S. Add diluted hydrochloric acid, dropwise, until the solution is acid to the indicator. Upon the addition of ammonium oxalate T.S., a white precipitate is formed. This precipitate is insoluble in acetic acid but dissolves in hydrochloric acid. Calcium salts moistened with hydrochloric acid impart a transient yellowish red color to a nonluminous flame.

Carbonate—Carbonates and bicarbonates effervesce with acids, evolving a colorless gas, which when passed into calcium hydroxide T.S. produces a white precipitate immediately. A cold solution of a soluble carbonate is colored red by phenolphthalein T.S., while a similar solution of a bicarbonate remains unchanged or is only slightly colored.

Chlorate—Solutions of chlorates yield no precipitate with silver nitrate T.S. The addition of sulfurous acid to this mixture produces a white precipitate which is insoluble in nitric acid but soluble in ammonia T.S. Upon ignition, chlorates yield chlorides, recognizable by appropriate tests. When sulfuric acid is added to a dry chlorate, decrepitation occurs and a greenish yellow gas is evolved. *Caution*—Use only a small amount of chlorate for this test and exercise extreme caution in performing it.

Chloride—Solutions of chlorides yield with silver nitrate T.S. a white, curdy precipitate, which is insoluble in nitric acid, but is soluble in a slight excess of ammonia T.S. When testing alkaloidal hydrochlorides, add ammonia T.S., filter, and acidify the filtrate with nitric acid, and proceed as directed above. Dry chlorides, when mixed with an equal weight of manganese dioxide, moistened with sulfuric acid, and gently heated evolve chlorine which is recognizable by its odor and by the production of a blue color with moistened starch iodide paper.

Citrate—Upon the addition of a few mg. of a citrate to a mixture of 15 ml. of pyridine and 5 ml. of acetic anhydride, a carmine red color is produced.

Cobalt—Solutions of cobaltous compounds yield a blue precipitate with sodium hydroxide T.S. This precipitate rapidly changes color, becoming olive-green, but if boiled soon after its formation, it becomes rose-red. Solutions of cobalt salts, when saturated with potassium chloride and treated with potassium nitrite and acetic acid, yield a yellow precipitate.

Copper—Solutions of cupric compounds, acidified with hydrochloric acid, deposit a red film of metallic copper upon a bright untarnished surface of metallic iron. An excess of ammonia T.S., added to a solution of a cupric salt, produces first a bluish precipitate and then a deep blue-colored solution. With potassium ferrocyanide T.S., solutions of cupric salts yield a reddish brown precipitate, insoluble in diluted acids.

Hypophosphite—When strongly heated, hypophosphites evolve spontaneously flammable phosphine. Hypophosphites in solution yield a white precipitate with mercuric chloride T.S. This precipitate becomes gray when an excess of hypophosphite is present. Solutions of hypophosphites, acidified with sulfuric acid and warmed with cupric sulfate T.S., yield a red precipitate.

Iodide—Solutions of iodides, upon the addition of chlorine T.S., dropwise, liberate iodine, which colors the solution yellow to red. When the solution is shaken with chloroform, the latter is colored violet. The iodine thus liberated gives a blue color with starch T.S. Silver nitrate T.S. produces in solutions of iodides a yellow, curdy precipitate, which is insoluble in nitric acid and in ammonia T.S.

Iron—Ferrous and ferric compounds in solution yield a black precipitate with ammonium sulfide T.S. This precipitate is dissolved by cold diluted hydrochloric acid with the evolution of hydrogen sulfide.

Ferric Salts—Acid solutions of ferric salts yield a dark blue precipitate with potassium ferrocyanide T.S. With an excess of sodium hydroxide T.S., a reddish brown precipitate is formed. Solutions of ferric salts produce with ammonium thiocyanate T.S. a deep red color which is not destroyed by diluted mineral acids.

Ferrous Salts—Solutions of ferrous salts yield a dark blue precipitate with potassium ferricyanide T.S. This precipitate is insoluble in diluted hydrochloric acid, but is decomposed by sodium hydroxide T.S. Solutions of ferrous salts yield with sodium hydroxide T.S. a greenish white precipitate, the color rapidly changing to green and then to brown when shaken.

Lactate—When solutions of lactates are acidified with sulfuric acid, and potassium permanganate T.S. is added and the mixture heated, acetaldehyde, recognizable by its distinctive odor, is evolved.

Lead—Solutions of lead salts yield with diluted sulfuric acid a white precipitate which is insoluble in diluted hydrochloric or nitric acid, but soluble in warm sodium hydroxide T.S. and in ammonium acetate T.S. With potassium chromate T.S., solutions of lead salts, free or nearly free from mineral acids, yield a yellow precipitate which is insoluble in acetic acid but soluble in sodium hydroxide T.S.

Lithium—Moderately concentrated solutions of lithium salts, made alkaline with sodium hydroxide, yield with sodium carbonate T.S. a white precipitate on boiling. The precipitate is soluble in ammonium chloride T.S. Lithium salts moistened with hydrochloric acid impart an intense crimson color to a nonluminous flame. Solutions of lithium salts are not precipitated by diluted sulfuric acid or soluble sulfates (difference from *strontium*).

Magnesium—Solutions of magnesium salts in the presence of ammonium chloride yield no precipitate with ammonium carbonate T.S., but on the subsequent addition of sodium phosphate T.S., a white, crystalline precipitate, which is insoluble in ammonia T.S., is formed.

Manganese—Solutions of manganous salts yield with ammonium sulfide T.S. a salmon-colored precipitate which dissolves in acetic acid.

Mercury—Solutions of mercury salts, free from an excess of nitric acid, when applied to bright copper foil, yield a deposit, which, upon rubbing, becomes bright and silvery in appearance. With hydrogen sulfide, solutions of mercury compounds yield a black precipitate which is insoluble in ammonium sulfide T.S. and in boiling diluted nitric acid.

Mercuric Salts—Solutions of mercuric salts yield a yellow precipitate with sodium hydroxide T.S. They yield also, in neutral solutions with potassium iodide T.S., a scarlet precipitate which is very soluble in an excess of the reagent.

Mercurous Salts—Mercurous compounds are decomposed by sodium hydroxide T.S., producing a black color. Solutions of mercurous salts yield with hydrochloric acid a white precipitate which is blackened by ammonia T.S. With potassium iodide T.S., a yellow precipitate, which may become green upon standing, is formed.

Nitrate—When a solution of a nitrate is mixed with an equal volume of sulfuric acid, the mixture cooled, and a solution of ferrous sulfate superimposed, a brown color is produced at the junction of the two liquids. When a nitrate is heated with sulfuric acid and metallic copper, brownish red fumes are evolved. Nitrates do not decolorize acidified potassium permanganate T.S. (distinction from *nitrites*).

Nitrite—When treated with diluted mineral acids or with acetic acid, nitrites evolve brownish red fumes. A few drops of potassium iodide T.S. and a few drops of diluted sulfuric acid, added to a solution of a nitrite, liberate iodine which colors starch T.S. blue.

Oxalate—Neutral and alkaline solutions of oxalates yield a white precipitate with calcium chloride T.S. This precipitate is insoluble in acetic acid but is dissolved by hydrochloric acid. Hot acidified solutions of oxalates decolorize potassium permanganate T.S.

Permanganate—Solutions of permanganates acidified with sulfuric acid are decolorized by hydrogen peroxide T.S. and by sodium bisulfite T.S., in the cold, and by oxalic acid T.S., in hot solution.

Peroxide—Solutions of peroxides slightly acidified with sulfuric acid yield a deep blue color upon the addition of potassium dichromate T.S. On shaking the mixture with an equal volume of ether and allowing the liquids to separate, the blue color will be found in the ether layer.

Phosphate—Neutral solutions of orthophosphates yield with silver nitrate T.S. a yellow precipitate, which is soluble in diluted nitric acid or in ammonia T.S. With ammonium molybdate T.S., a yellow precipitate, which is soluble in ammonia T.S., is formed.

Potassium—Potassium compounds impart a violet color to a nonluminous flame, but the presence of small quantities of sodium masks the color. In neutral, concentrated or moderately concentrated solutions of potassium salts (depending upon the solubility and the potassium content), sodium bitartrate T.S. produces a white, crystalline precipitate soluble in ammonia T.S. and in solutions of alkali hydroxides and carbonates. The formation of the precipitate, which is usually slow, is accelerated by stirring or rubbing the inside of the test tube with a glass rod. The addition of a little glacial acetic acid or alcohol also promotes the precipitation.

Salicylate—In moderately dilute solutions of salicylates, ferric chloride T.S. produces a violet color. The addition of acids to moderately concentrated solutions of salicylates produces a white, crystalline precipitate of salicylic acid, which melts between 158° and 161°.

Silver—Solutions of silver salts yield with hydrochloric acid a white, curdy precipitate, which is insoluble in nitric acid but is readily soluble in ammonia T.S. A solution of a silver salt to which ammonia T.S. and a small quantity of formaldehyde T.S. are added deposits, upon warming, a mirror of metallic silver upon the sides of the container.

Sodium—Solutions of sodium compounds after conversion to chloride or nitrate yield, with five times their volume of cobalt-uranyl acetate T.S., a golden-yellow precipitate, which forms after agitation for several minutes. Sodium compounds impart an intense yellow color to a nonluminous flame.

Sulfate—Solutions of sulfates yield with barium chloride T.S. a white precipitate, which is insoluble in hydrochloric and in nitric acid. With lead acetate T.S., sulfates yield a white precipitate soluble in ammonium acetate solution. Hydrochloric acid produces no precipitate when added to solutions of sulfates (distinction from *thiosulfates*).

Sulfite—When treated with diluted hydrochloric acid, sulfites and bisulfites yield sulfur dioxide, recognizable by its characteristic, pungent odor. This gas blackens filter paper moistened with mercurous nitrate T.S.

Tartrate—Upon the addition of a few mg. of a tartrate to a mixture of 15 ml. of pyridine and 5 ml. of acetic anhydride, an emerald green color is produced.

Thiocyanate—Solutions of thiocyanates yield with ferric chloride T.S. a red color which is not destroyed by moderately concentrated mineral acids.

Thiosulfate—Solutions of thiosulfates yield with hydrochloric acid a white precipitate which soon turns yellow, and sulfur dioxide is liberated, recognizable by its odor. The addition of ferric chloride T.S. to solutions of thiosulfates produces a dark violet color which quickly disappears.

Zinc—In the presence of sodium acetate, solutions of zinc salts yield a white precipitate with hydrogen sulfide. This precipitate is insoluble in acetic acid but is dissolved by diluted hydrochloric acid. Ammonium sulfide T.S. produces a similar precipitate in neutral and in alkaline solutions. Zinc salts in solution yield with potassium ferrocyanide T.S. a white precipitate which is insoluble in diluted hydrochloric acid.

IDENTIFICATION—ORGANIC NITROGENOUS BASES

Dissolve 50 mg. of the specified salt of the organic nitrogenous base, if in bulk, in 25 ml. of water, or shake a quantity of powdered tablets or the contents of capsules equivalent to 50 mg. of the salt with 25 ml. of 0.01 N hydrochloric acid for 10 minutes. Transfer the liquid to a separator if necessary, filtering it and washing the filter and the residue with several small portions of water. In a second separator dissolve 50 mg. of the corresponding Reference Standard in 25 ml. of water. Treat each solution as follows: Add 2 ml. of sodium hydroxide T.S. and 4 ml. of carbon disulfide, and shake for 2 minutes. Centrifuge if necessary to clarify the lower phase, and filter it through a dry filter, collecting the filtrate in a small flask provided with a glass stopper. Without delay determine the absorption spectra of the filtered solutions of both standard and sample, in 1-mm. cells between 7 μ and 15 μ, with a suitable infrared spectrophotometer, using carbon disulfide in a matched cell as the blank. The spectrum of the solution prepared from the sample shows all of the significant absorption bands present in the spectrum of the solution prepared from the Reference Standard. If the spectrum of the sample preparation possesses obscuring absorption bands not present in that of the standard preparation, the sample should be further purified and the test repeated (see page 872).

INJECTIONS

Every care should be exercised in the preparation of all products intended for injection, to prevent contamination with microorganisms and foreign material. Good pharmaceutical practice requires also that each Injection, in its final container, be subjected individually to a physical inspection, whenever the construction of the container permits.

Definitions—In this National Formulary, the sterile preparations for parenteral use are grouped in five distinct classes, defined as follows: (1) Solutions of medicaments suitable for injection, referred to by titles of the form, ——*Injection;* (2) dry solids which, upon the addition of suitable solvents, yield solutions conforming in all respects to the requirements for Injections, and which are distinguished by titles of the form, ——*for Injection* or *Sterile*——, depending upon whether buffers, diluents, etc., are present; (3) solids which are suspended in a suitable fluid medium and which are not to be injected intravenously or into the spinal canal, distinguished by titles of the form, *Sterile——Suspension;* (4) dry solids which, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Sterile Suspensions, and which are distinguished by titles of the form, *Sterile ——for Suspension;* and (5) emulsions of fluids in fluid media, suitable for parenteral administration, which are not to be injected into the spinal canal, and which are distinguished by titles of the form, *Sterile——Emulsion.*

Aqueous Vehicles—The vehicles for aqueous Injections meet the requirements under *Pyrogen Test,* page 851. *Water for Injection,* USP XVIII, is generally used as the vehicle for an aqueous Injection, unless otherwise specified in the individual monograph. Sodium chloride may be added in amounts sufficient to render the resulting solution isotonic; and *Sodium Chloride Injection,* USP XVIII, or *Ringer's Injection,* USP XVIII, may be used in whole or in part instead of *Water for Injection* unless otherwise specified in the individual monograph. For conditions applying to other adjuvants, see *Added Substances,* in this chapter. Aqueous vehicles used in products that cannot in finished form be tested for pyrogens meet the requirements under *Pyrogen Test,* page 851.

Other Vehicles—Fixed oils used as vehicles for nonaqueous Injections are of vegetable origin, are odorless or nearly so, and have no odor or taste suggesting rancidity. They meet the requirements of the test for *Solid paraffin* under *Light Mineral Oil,* page 461, the cooling bath being maintained at 10°, have a *Saponification value* of not less than 185 and not more than 200 (see page 805), have an *Iodine value* of not less than 79 and not more than 128 (see page 804), and meet the requirements of the following tests:

Unsaponifiable Matter—Heat on a steam bath 10 ml. of the oil with 15 ml. of sodium hydroxide solution (1 in 6) and 30 ml. of alcohol in a flask having a small, short-stemmed funnel inserted in the neck, and occasionally agitate the mixture until it becomes clear. Transfer the solution to a shallow dish, evaporate the alcohol on a steam bath, and mix the residue with 100 ml. of water: a clear solution results.

Free Fatty Acids—The free fatty acids in 10 g. of oil require for neutralization not more than 2 ml. of 0.02 *N* sodium hydroxide.

Synthetic mono- or di-glycerides of fatty acids may be used as vehicles, provided they are liquid and remain clear when cooled to 10° and have an *Iodine value* of not more than 140 (see page 804).

These and other nonaqueous vehicles may be used, provided they are safe in the volume of Injection administered, and also provided they do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests. Such vehicles may be used alone or in combination with aqueous or other vehicles.

Added Substances—Suitable substances may be added to preparations intended for injection to increase stability or usefulness, unless prescribed in the individual monograph, provided they are harmless in the amounts administered and do not interfere with the therapeutic efficacy or with the responses to the specified assays and tests. No coloring agent may be added, solely for the purpose of coloring the finished preparation, to a solution intended for parenteral administration. (See also *Added Substances* under *General Notices,* page 7.)

Observe special care in the choice and usage of added substances in preparations for injection which are administered in a volume exceeding 5 ml. The following maximum limits prevail unless otherwise directed: for agents containing mercury and the cationic, surface-active compounds, 0.01 percent; for those of the type of chlorobutanol, cresol, and phenol, 0.5 percent; and for sulfur dioxide, or an equivalent amount of sodium bisulfite or sodium sulfite, 0.2 percent.

A suitable substance or mixture of substances to prevent the growth of microorganisms should be added to preparations intended for injection that are packaged in multiple-dose containers, regardless of the method of sterilization employed, unless otherwise directed in the individual monograph, or unless the active ingredients are themselves bacteriostatic. Such substances are used in concentrations that will prevent the growth of or kill microorganisms in the preparations for injection. Sterilization processes are employed even though such substances are used (see also *General Notices,* page 8). The air in the container may be evacuated or be displaced by a chemically inert gas.

Containers for Injections—Containers, including the closures, for preparations for injection do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. If the container is made of glass, it is clear and colorless or of light amber color and permits inspection of its contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Plastic containers meeting the requirements under *Plastics—Containers for Injections,* page 840, may be used instead of glass unless otherwise stated in the individual monograph.

For definitions of single-dose and multiple-dose containers, see *Containers* under *General Notices,* page 12. Glass containers meet the requirements under *Containers—Glass,* page 785.

Containers are closed by fusion, or by application of suitable closures, in such manner as to prevent contamination or loss of contents. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a sharp needle without detachment of fragments, and upon withdrawal of the needle at once recloses the container against contamination.

Containers for Sterile Solids—Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such a manner that the sterility of the product is maintained.

Volume in Container—Each container of an Injection contains a volume in slight excess of the labeled "size" or that which is to be withdrawn. The excess volumes recommended in the following table are usually sufficient to permit withdrawal and administration of the labeled volumes.

Recommended Overages

Labeled Size	Excess Volume for Mobile Liquids	Excess Volume for Viscous Liquids
0.5 ml.	0.10 ml.	0.12 ml.
1.0 ml.	0.10 ml.	0.15 ml.
2.0 ml.	0.15 ml.	0.25 ml.
5.0 ml.	0.30 ml.	0.50 ml.
10.0 ml.	0.50 ml.	0.70 ml.
20.0 ml.	0.60 ml.	0.90 ml.
30.0 ml.	0.8 ml.	1.2 ml.
50.0 ml. or more	2 percent	3 percent

Determination of Volume of Injection in Containers—Select 1 or more containers if the volume is 10 ml. or more, 3 or more if the volume is more than 3 ml. and less than 10 ml., or 5 or more if the volume is 3 ml. or less. Take up individually the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured, and fitted with a 21-gauge needle not less than 2.5 cm. (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the total volume to be measured occupies at least 40 percent of its rated volume. The contents of two or three 1-ml. or 2-ml. containers may be pooled for measurement provided that a separate, dry syringe assembly is used for each container.

For parenterals in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified.

The contents of single-dose containers or multiple-dose containers other than those described above, holding 10 ml. or more may be determined by opening them and emptying the contents directly into the graduated cylinder instead of transferring the contents by means of a syringe.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents.

Limits—The volume at 25° is not less than the labeled volume in the case of containers examined individually or, in the case of 1-ml. and 2-ml. containers, not less than the sum of the labeled volumes of the containers taken collectively.

Sterility Tests—Preparations for injection meet the requirements under *Sterility Tests,* page 874.

Labeling—The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of a preparation or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

The label upon each immediate container of a preparation for injection states the contents of the container, the name of the preparation, the recommended or usual dose, the route of administration, the quantity or proportion of each active and inactive ingredient (except that ingredients added to adjust the pH or to make the solution isotonic may be declared by name and a statement of their effect), and the storage statement and expiration date when required by the individual monograph; if the vehicle is *Water for injection,* it need not be named. The volume of liquid to be added to prepare an Injection or Suspension from a dry preparation may be given in the labeling. Also, the label indicates the name of the manufacturer and the manufacturer's identifying lot number. The lot number is capable of yielding the complete manufacturing history of the specific package, including any single manufacturing, filling, and sterilizing operation. For containers too small to accommodate a label of sufficient size, the required information—other than the contents of the container, the name of the preparation, the quantity or proportion of each active ingredient, and the manufacturer's name and lot number—may be contained in other labeling.

The container is so labeled that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

The labeling on or within the package bears adequate information for the use of the preparation, including the same information regarding ingredients that appears on the label of the immediate container, plus information regarding indications, contraindications, side-effects, any relevant hazards, dosage, and routes, methods, frequency, and duration of administration. This labeling bears a date of issue.

Injections packaged for use as irrigation solutions meet the requirements for Injections, except those relating to packaging, since their containers may be designed to empty rapidly and may exceed one liter capacity. Injections packaged in larger than one-liter containers are labeled for use as irrigation fluids only and bear label statements to the effect that such packages are not intended for use in administering the contents by intravenous infusion.

Packaging and Storage—The volume of Injection in single-dose containers provides the amount specified for parenteral administration at one time and, except for irrigation solutions, is not more than sufficient to permit the withdrawal and administration of one liter.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, no multiple-dose container contains a volume of Injection more than sufficient to permit the withdrawal of 30 ml.

LEAD LIMIT TEST

Select all reagents for this test to have as low a content of lead as practicable, and store all reagent solutions in containers of borosilicate glass. Rinse thoroughly all glassware with warm dilute nitric acid (1 in 2), followed by water.

Special Reagents—

Ammonia-Cyanide Solution—Dissolve 2 g. of potassium cyanide in 15 ml. of stronger ammonia water, and dilute with water to 100 ml.

Ammonium Citrate Solution—Dissolve 40 g. of citric acid in 90 ml. of water. Add 2 or 3 drops of phenol red T.S., then cautiously add stronger ammonia water until the solution acquires a reddish color. Remove any lead that may be present by extracting the solution with 20-ml. portions of *Dithizone Extraction Solution* (see below), until the dithizone solution retains its orange-green color.

Diluted Standard Lead Solution—Dilute 10.0 ml. of *Standard Lead Solution*, page 806 (containing 10 mcg. of lead per ml.) with sufficient dilute nitric acid (1 in 100) to make 100.0 ml. This solution contains 1 mcg. of lead per ml.

Dithizone Extraction Solution—Dissolve 30 mg. of dithizone in 1000 ml. of chloroform, and add 5 ml. of alcohol. Store the solution in a refrigerator.

Before use, shake a suitable volume of the *Dithizone Extraction Solution* with about half its volume of dilute nitric acid (1 in 100), discarding the nitric acid.

Hydroxylamine Hydrochloride Solution—Dissolve 20 g. of hydroxylamine hydrochloride in sufficient water to make approximately 65 ml. Transfer to a separator, add a few drops of thymol blue indicator T.S., then add stronger ammonia water until the solution assumes a yellow color. Add 10 ml. of sodium diethyldithiocarbamate solution (1 in 25), mix, and allow to stand for 5 minutes. Extract this solution with successive 10 to 15-ml. portions of chloroform until a 5-ml. portion of the chloroform extract does not assume a yellow color when shaken with a dilute cupric sulfate solution. Add diluted hydrochloric acid until the solution is pink (if necessary, add 1 or 2 drops more of thymol blue indicator T.S.), and then dilute with water to 100 ml.

Nitric Acid (1 in 100)—Dilute 10 ml. of nitric acid with sufficient water to make 1000 ml.

Potassium Cyanide Solution—Dissolve 50 g. of potassium cyanide in sufficient water to make 100 ml. Remove the lead from this solution by extraction with successive portions of *Dithizone Extraction Solution*, as described under *Ammonium Citrate Solution* above, then extract any dithizone remaining in the cyanide solution by shaking with chloroform. Finally dilute the cyanide solution with sufficient water so that each 100 ml. contains 10 g. of potassium cyanide.

Standard Dithizone Solution—Dissolve

10 mg. of dithizone in 1000 ml. of chloroform. Keep the solution in a glass-stoppered, lead-free bottle, suitably wrapped to protect it from light, and store in a refrigerator.

Procedure—Transfer the volume of the prepared sample directed in the monograph to a separator, and, unless otherwise directed in the monograph, add 6 ml. of *Ammonium Citrate Solution*, 2 ml. of *Potassium Cyanide Solution* and 2 ml. of *Hydroxylamine Hydrochloride Solution*. (For the determination of lead in iron salts use 10 ml. of *Ammonium Citrate Solution*.) Add 2 drops of phenol red T.S., and make the solution just alkaline (red in color) by the addition of stronger ammonia water. Immediately extract the solution with 5-ml. portions of *Dithizone Extraction Solution*, draining off the extracts into another separator, until the dithizone solution retains its green color. Shake the combined dithizone solutions for 30 seconds with 20 ml. of dilute nitric acid (1 in 100), and discard the chloroform layer. Add to the acid solution 5.0 ml. of *Standard Dithizone Solution* and 4 ml. of *Ammonia-Cyanide Solution*, and shake for 30 seconds: the color of the chloroform layer is of no deeper shade of violet than that of a control made with a volume of *Diluted Standard Lead Solution* equivalent to the amount of lead permitted in the sample under examination and the same quantities of the same reagents and in the same manner as the test with the sample.

LOSS ON DRYING

The procedure set forth in this chapter determines the amount of volatile matter driven off under the conditions specified, and such matter may include material other than adsorbed moisture. For substances appearing to contain water as the only volatile constituent, the procedure given on page 900 is appropriate and is specified in the monograph.

Unless otherwise directed in the monograph, conduct the determination on 1 to 2 g. of the substance, previously mixed and accurately weighed. If the sample is in the form of large crystals, reduce the particle size to about 2 mm. by quickly crushing. Tare a glass-stoppered, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the sample in the bottle, replace the cover and weigh the bottle and the contents. By gentle, sidewise shaking distribute the sample as evenly as practicable to a depth of about 5 mm. generally, and not over 10 mm. in the case of bulky materials. Place the loaded bottle in the drying chamber, removing the stopper and leaving it also in the chamber, and dry the sample at the temperature and for the time specified in the monograph. Upon opening the chamber, close the bottle promptly and allow it to come to room temperature before weighing.

If the substance melts at a lower temperature than that specified for the determination of *Loss on drying*, expose the bottle with its contents for 1 to 2 hours to a temperature 5° to 10° below the melting temperature, then dry at the specified temperature.

When drying in a desiccator is specified, exercise particular care to ensure that the desiccant is kept fully effective by frequent replacement.

MELTING RANGE OR TEMPERATURE

For National Formulary purposes, the melting range or temperature of a solid is defined as those points of temperature within which, or the point at which, the solid coalesces and is completely melted, when determined as directed below. An apparatus or method capable of equal accuracy may be used. The accuracy should be checked frequently by the use of one or more of the six USP Melting Point Reference Standards, preferably the one that melts nearest the melting temperature of the compound to be tested.

Five procedures for the determination of melting range or temperature are given herein, varying in accordance with the nature of the substance. When no class is designated in the monograph, use the procedure for *Class I*.

The procedure known as the mixed-melting point determination, whereby the melting range of a solid under test is compared with that of an intimate mixture of equal parts of the solid and an authentic specimen of it, such as the corresponding NF or USP Reference Standard, may be used as a confirmatory identification test. Agreement of the observations on the original and the mixture constitutes evidence of chemical identity.

Apparatus—A suitable melting range apparatus consists of a glass container for a bath of substantially transparent fluid, a suitable stirring device, an accurate thermometer (see page 880), and a controlled source of heat. The bath fluid is selected with a view to the temperature required, but light paraffin is used generally and certain liquid silicones are well adapted to the higher temperature ranges. The fluid is deep enough to permit immersion of the thermometer to its specified immersion depth so that the bulb is still about 2 cm. above the bottom of the bath. The heat may be supplied by an open flame or electrically. The capillary tube is about 10 cm. long and 0.8 to 1.2 mm. in internal diameter with walls 0.2 to 0.3 mm. in thickness.

The thermometer is preferably Type I or Type II (see page 880), selected for the desired range or temperature.

Procedure for Class I—Reduce the sample to a very fine powder, and, unless otherwise directed, render it anhydrous when it contains water of hydration by drying it at the temperature specified in the monograph, or, when the substance contains no water of hydration, dry it over a suitable desiccant for 24 hours.

Charge a capillary glass tube, one end of which is sealed, with sufficient of the dry powder to form a column in the bottom of the tube 2.5 to 3.5 mm. high when packed down as closely as possible by moderate tapping on a solid surface.

Heat the bath until a temperature approximately 30° below the expected melting point is reached, attach the capillary tube to the thermometer by wetting both with a drop of the liquid of the bath or otherwise, and adjust its height so that the material in the capillary is level with the thermometer bulb. Return the thermometer to the bath, continue the heating, with constant stirring, at a rate of rise of approximately 3° per minute until a temperature 3° below the expected melting point is attained, then carefully regulate the rate to about 1° to 2° per minute until melting is complete.

The temperature at which the column of the sample is observed to collapse definitely against the side of the tube at any point is defined as the beginning of melting, and the temperature at which the sample becomes liquid throughout is defined as the end of melting. The two temperatures fall within the limits of the melting range.

Procedure for Class Ia—Reduce the sample to a very fine powder, and, unless otherwise directed, render it anhydrous when it contains water of hydration by drying it at the temperature specified in the monograph, or, when the substance contains no water of hydration, dry it over a suitable desiccant for not less than 16 hours.

Charge a capillary glass tube, one end of which is sealed, with sufficient of the dry powder to form a column in the bottom of the tube 2.5 to 3.5 mm. high when packed down as closely as possible by moderate tapping on a solid surface.

Heat the bath until a temperature approximately 10° below the expected melting point is reached, then adjust the rate of heating to a rise of 1 ± 0.5° per minute. When the temperature is about 5° below the lower limit of the expected melting range, remove the thermometer, and quickly attach the capillary tube to the thermometer by wetting both with a drop of the liquid of the bath or otherwise, and adjust its height so that the material in the capillary is level with the thermometer bulb. Replace the thermometer, and continue the heating until melting is completed.

The temperature at which the column of the sample is observed to collapse definitely against the side of the tube at any point is defined as the beginning of melting, and the temperature at which the sample becomes liquid throughout is defined as the end of melting or the "melting point." The two temperatures fall within the limits of the melting range.

Procedure for Class Ib—Place the sample in a closed container and cool to 10°, or lower, for at least 2 hours. Without previous powdering, charge the cooled material into the capillary tube as directed for *Class I*, then immediately place the charged tube in a vacuum desiccator and dry at a pressure not exceeding 20 mm. of mercury for 3 hours. Immediately upon removal from the desiccator, fire-seal the open end of the tube, and as soon as practicable proceed with the determination of the melting range as directed under *Class Ia*, beginning with "Heat the bath."

If the particle size of the material is too large for the capillary, pre-cool the sample as above directed, then with as little pressure as possible gently crush the particles to fit the capillary, and immediately charge the tube.

Procedure for Class II—Carefully melt the material to be tested at as low a temperature as possible, and draw it into a capillary tube, which is left open at both ends, to a depth of about 10 mm. Cool the charged tube at 10°, or lower, for 24 hours, or in contact with ice for at least 2 hours. Then attach the tube to the thermometer by suitable means, adjust it in a water bath so that the upper edge of the material is 10 mm. below the water level, and heat as directed for *Class I* except, within 5° of the expected melting temperature, regulate the rate of rise of temperature to 0.5° to 1.0° per minute. The temperature at which the material is observed to rise in the capillary tube is the melting temperature.

Procedure for Class III—Melt a quantity of the substance slowly, while stirring, until it reaches a temperature of 90° to 92°. Remove the source of heat and allow the molten substance to cool to a temperature of 8° to 10° above the expected melting point. Chill the bulb of a Type III thermometer (see page 880) to 5°, wipe it dry, and while it is still cold dip it into the molten substance so that approximately the lower half of the bulb is submerged. Withdraw it immediately, and hold it vertically away from the heat until the wax surface dulls, then dip it for 5 minutes into a water bath having a temperature not higher than 16°.

Fix the thermometer securely in a test tube so that the lower point is 15 mm. above the bottom of the test tube. Suspend the test tube in a water bath adjusted to about 16°, and raise the temperature of the bath at the rate of 2° per minute to 30°, then change to a rate of 1° per minute, and note the temperature at which the first drop of melted substance leaves the thermometer. Repeat the determination twice on a freshly melted portion of the sample. If the variation of three determinations is less than 1°, take the average of the three as the melting point. If the variation of three determinations is greater than 1°, make two additional determinations and take the average of the five.

MERCURY LIMIT TEST

The mercury limit test is designed to determine the limit of mercury as a trace impurity.

Reagents—

Dithizone Stock Solution—Dissolve 40 mg. of dithizone in 1000 ml. of chloroform.

Dithizone Titrating Solution—Dilute 30.0 ml. of *Dithizone Stock Solution* to 100.0 ml. with chloroform. This solution contains approximately 12 mg. per liter.

Mercury Standard Stock Solution—Transfer 135.4 mg. of mercuric chloride to a 100-ml. volumetric flask and dilute to volume with approximately 1 *N* sulfuric acid. This solution contains the equivalent of 100 mg. of Hg in 100 ml.

Mercury Solution for Standardizing Dithizone Titrating Solution—Pipet 2.0 ml. of *Mercury Standard Stock Solution* into a 100-ml. volumetric flask, and dilute to volume with approximately 1 *N* sulfuric acid. Each ml. of this solution contains the equivalent of 20 mcg. of Hg.

Standardization of Dithizone Titrating Solution—Pipet 1.0 ml. of *Mercury Solution for Standardizing Dithizone Titrating Solution* into a 250-ml. separator, add 100 ml. of 1 *N* sulfuric acid, 90 ml. of water, and 10 ml. of hydroxylamine hydrochloride solution (1 in 5). To the solution add *Dithizone Titrating Solution* from a 10-ml. microburet in small portions. Shake the mixture exactly 20 times after each addition, allow the chloroform layers to separate, and then discard. Continue until a final addition of *Dithizone Titrating Solution* is green in color after shaking. Calculate the mcg. of mercury equivalent to 1 ml. of *Dithizone Titrating Solution* by dividing 20 by the number of ml. of *Dithizone Titrating Solution* added.

Preparation of Sample—Transfer 2 g. of the sample, accurately weighed, into a 250-ml. glass-stoppered conical flask, add 20 ml. of a mixture of equal volumes of nitric acid and sulfuric acid, attach a suitable condenser, reflux the mixture for 1 hour, cool, cautiously dilute with water, and boil until fumes of nitrous acid are no longer noticeable. Cool the solution, cautiously dilute with water, transfer it to a 200-ml. volumetric flask, dilute to volume with water, mix, and filter.

Titration of Sample—Pipet 50.0 ml. of the prepared sample into a 250-ml. separator, and extract with successive small portions of chloroform until the chloroform extract remains colorless. Discard the chloroform extract, and add to the sample 50 ml. of 1 *N* sulfuric acid, 90 ml. of water, and 10 ml. of hydroxylamine hydrochloride solution (1 in 5). Proceed as directed in the *Standardization of Dithizone Titrating Solution*. Titrate until a final addition remains green in color and calculate the amount of mercury in the sample.

Note: Mercuric dithizonate is light-sensitive. This test should be performed in subdued light. The addition of acetic acid to the titration mixture helps to stabilize mercuric dithizonate.

METAL PARTICLES—OPHTHALMIC OINTMENTS

Select a representative sample of 10 tubes of the Ointment, and extrude the contents of each tube as completely as practicable into separate 60-mm. cylinder plates (Petri dishes), the bottom halves of which measure about 50-mm. in internal diameter and are clear and free from scratches. Cover the dishes, and heat at 80° to 85° for 2 hours, unless other heating conditions are specified in the individual monograph. Allow the samples to cool to room temperature without agitation to allow free settling of any metal particles in the Ointment.

Remove the covers from the dishes, and invert each dish on the stage of a suitable microscope previously adjusted to provide about 30× magnification and equipped with an eyepiece micrometer disk which has been calibrated at the magnification employed. In addition to any desired substage illumination, each dish is illuminated from above by the beam from a Nicholas-type lamp placed at an angle of about 45° relative to the plane of the dish.

Examine the entire bottom of each dish for metal particles, and record the total number of particles measuring 50 μ or more in any dimension. The requirement is met if (1) a total of not more than 50 metal particles each measuring 50 μ or more in any dimension is found in the 10 tubes, and (2) not more than 1 tube is found to contain more than 8 such particles.

If the Ointment fails the above test, repeat the test on 20 additional representative tubes of the Ointment. The requirement is met if (1) a total of not more than 150 metal particles each measuring 50 μ or more in any dimension is found in the 30 tubes, and (2) not more than 3 tubes are found to contain more than 8 such particles each.

METHOXY DETERMINATION

Apparatus—The apparatus for methoxy determination is shown diagrammatically in the accompanying figure. The boiling flask, *A*, is fitted with a capillary side-arm for the introduction of carbon dioxide and is connected to a column, *B*, which serves to separate aqueous hydriodic acid from the more volatile methyl iodide. The methyl iodide passes through water in a scrubber trap, *C*, and is finally absorbed in the bromine-acetic acid solution in absorption tube *D*. The carbon dioxide is introduced from a device arranged to minimize pressure fluctuations and connected to the apparatus by a small capillary containing a small cotton pledget.

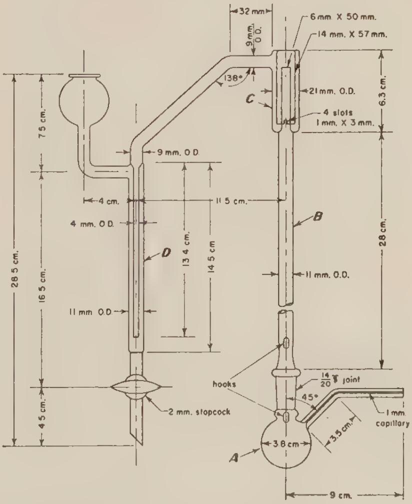
Reagents—

Potassium Acetate in Acetic Acid—Dissolve 100 g. of potassium acetate in 1000 ml. of a solution consisting of 900 ml. of glacial acetic acid and 100 ml. of acetic anhydride.

Bromine-Acetic Acid Solution—Dissolve 5 ml. of bromine in 145 ml. of the *Potassium Acetate in Acetic Acid* solution. Prepare this solution fresh daily.

Hydriodic Acid for Methoxy Determination—This may be prepared by distilling hydriodic acid over red phosphorus, passing carbon dioxide through the apparatus during the distillation. The constant boiling mixture (between 55 and 58 percent HI) distilling over at 126° to 127°, which is colorless or nearly colorless, is used. Place the acid in small, brown, glass-stoppered bottles previously swept out with carbon dioxide, seal with paraffin, and store in a cool, dark place. (*Caution: Use safety precautions when distilling hydriodic acid.*)

Procedure—Prepare the apparatus by placing in trap *C*, through the funnel on tube *D* and the connecting side-arm, a volume sufficient to make trap *C* half-full of water. Add 7 ml. of *Bromine-Acetic Acid Solution* to absorption tube *D*. Weigh the sample, previously dried at 105° for 2 hours, in a tared gelatin capsule, and add it to the boiling flask along with a few glass beads or pieces of porous plate. Finally add 6 ml. of *Hydriodic Acid* and attach the flask to the condenser, using a few drops of the acid to seal the junction. Bubble the carbon dioxide through the apparatus at the rate of about 2 bubbles per second, place the boiling flask in an oil bath heated to 150°, and continue the reaction for 40 minutes. Drain the contents of the absorption tube into a 500-ml. conical flask containing 10 ml. of sodium acetate solution (1 in 4). Rinse the tube with water, adding the rinsings to the flask, and finally dilute with water to about 125 ml. Add formic acid, dropwise, with swirling, until the reddish brown color of the bromine is discharged, then add 3 additional drops. A total of 12 to 15 drops usually is required. Let stand for 3 minutes, and add 15 ml. of diluted sulfuric acid and 3 g. of potassium iodide, and titrate immediately with 0.1 *N* sodium thiosulfate to the sharp disappearance of the yellow iodine color, using starch T.S. to confirm the end-point. Perform a blank determination, including a gelatin capsule, and make any necessary correction. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 517 mcg. of (OCH_3).



Apparatus for Methoxy Determination

NIACIN OR NIACINAMIDE ASSAY

Chemical Method

[Note—Determine from the labeling if the vitamin in the sample is niacin or niacinamide, and use the corresponding standard preparation (either *Standard Niacin Preparation* or *Standard Niacinamide Preparation*) as directed in the *Procedure*.]

Cyanogen Bromide Solution—Dissolve 5 g. of cyanogen bromide in water to make 50 ml. *Caution—Prepare this solution under a hood,* as cyanogen bromide volatilizes at room temperature and the vapor is highly irritating and *poisonous.*

Sulfanilic Acid Solution—To 2.5 g. of sulfanilic acid add 15 ml. of water and 3 ml. of ammonia T.S. Mix, add, with stirring, more ammonia T.S. if necessary until the acid dissolves, adjust the pH of the solution to about 4.5 with diluted hydrochloric acid, using bromocresol green T.S. as an outside indicator, and dilute with water to 25 ml.

Standard Niacin Stock Solution—Dissolve 50.0 mg. of NF Niacin Reference Standard, previously dried and stored, protected from light, in a desiccator over phosphorus pentoxide, in sufficient alcohol solution (1 in 4) to make 500.0 ml. Store in a refrigerator. Each ml. of this solution contains 100 mcg. of NF Niacin Reference Standard.

Standard Niacin Preparation—Transfer 10.0 ml. of *Standard Niacin Stock Solution* to a 100-ml. volumetric flask; dilute to volume with water, and mix. Each ml. of this solution contains 10 mcg. of NF Niacin Reference Standard.

Standard Niacinamide Stock Solution—Dissolve 50.0 mg. of USP Niacinamide Reference Standard, previously dried and stored, protected from light, in a desiccator over phosphorus pentoxide, in sufficient alcohol solution (1 in 4) to make 500.0 ml. Store in a refrigerator. Each ml. of this solution contains 100 mcg. of USP Niacinamide Reference Standard.

Standard Niacinamide Preparation—Transfer 10.0 ml. of *Standard Niacinamide Stock Solution* to a 100-ml. volumetric flask, dilute to volume with water, and mix. Each ml. of this solution contains 10 mcg. of USP Niacinamide Reference Standard.

Sample Preparation—Prepare as directed in the individual monograph.

Procedure—Pipet into four marked tubes the quantities of the appropriate *Standard Preparation,* the *Assay Preparation,* the ammonia dilution, and water indicated in the accompanying table. Then add the other constituents respectively as listed in the table, according to the directions given herein.

To Tube 1 add the *Sulfanilic Acid Solution,* shake well, add the hydrochloric acid, mix, place in a suitable spectrophotometer and adjust to zero absorbance at 450 mμ. To Tube 2 add the *Cyanogen Bromide Solution,* mix, and exactly 30 seconds after completion of the addition of the cyanogen bromide add the *Sulfanilic Acid Solution,* with swirling. Close the tube, place it in the spectrophotometer, and after 2 minutes measure its absorbance at 450 mμ against Tube 1 as a blank, designating the absorbance as A_S. Repeat the procedure with Tubes 3 (as blank) and 4, designating the absorbance of Tube 4 as A_U. Calculate the quantity of niacin or niacinamide in the sample as directed in the individual monograph.

Microbiological Method

Test Solution of the Material to be Assayed—Place the prescribed amount of the material to be assayed in a flask of suitable size, and proceed by one of the methods given below. The concentrations of the sulfuric acid and sodium hydroxide solutions used are not stated in each instance because these concentrations may be varied depending upon the amount of material taken for assay, volume of test solution, and buffering effect of material.

(*a*) *For Dry or Semidry Materials That Contain No Appreciable Amount of Basic Substances*—Add a volume of 1 *N* sulfuric acid equal in ml. to not less than ten times the dry weight of the material in g., but the resulting solution shall contain not

Reaction Mixtures for Niacin or Niacinamide Assay—Chemical Assay

Constituent	Tube 1, ml.	Tube 2, ml.	Tube 3, ml.	Tube 4, ml.
Standard Preparation	1.0	1.0	. . .	. . .
Sample Preparation	. . .	. . .	1.0	1.0
Ammonia dilution (stronger ammonia water, diluted to 1 in 50)	0.5	0.5	0.5	0.5
Water	6.5	1.5	6.5	1.5
Cyanogen Bromide Solution	. . .	5.0	. . .	5.0
Sulfanilic Acid Solution	2.0	2.0	2.0	2.0
Hydrochloric acid	1 drop	. . .	1 drop	. . .

more than 5.0 mg. of niacin per ml. If the material is not readily soluble, comminute it so that it may be evenly dispersed in the liquid, then agitate vigorously and wash down the sides of the flask with 1 *N* sulfuric acid.

Heat the mixture in an autoclave at 121° to 123° for 30 minutes, and cool. If lumping occurs, agitate the mixture until the particles are evenly dispersed. Adjust the mixture to a pH of 6.8 with sodium hydroxide solution, dilute with water to make a final measured volume that contains a concentration of niacin equivalent to that of *Standard Niacin Solution*, and filter.

(*b*) *For Dry or Semidry Materials That Contain Appreciable Amounts of Basic Substances*—Add sufficient sulfuric acid solution to bring the pH of the mixture to between 5.0 and 6.0. Add such an amount of water that the total volume of liquid shall be equal in ml. to not less than ten times the dry weight of the sample in g., but the resulting solution shall contain not more than 5.0 mg. of niacin in each ml. Then add the equivalent of 10 ml. of 10 *N* sulfuric acid for each 100 ml. of liquid and proceed as directed under (*a*), beginning with the second paragraph.

(*c*) *For Liquid Materials*—Adjust the material to a pH of 5.0 to 6.0 with either sulfuric acid solution or sodium hydroxide solution. Add such an amount of water that the total volume of liquid shall be equal, in ml., to not less than 10 times the volume of the sample, in ml., but the resulting solution shall contain not more than 5.0 mg. of niacin in each ml. Then add the equivalent of 10 ml. of 10 *N* sulfuric acid for each ml. of liquid, and proceed as directed under (*a*), beginning with the second paragraph.

Standard Niacin Stock Solution I—Dissolve 50.0 mg. of NF Niacin Reference Standard, previously dried and stored in the dark in a desiccator over phosphorus pentoxide, in sufficient alcohol to make 500.0 ml. Store in a refrigerator. Each 1.0 ml. represents 100.0 mcg. of NF Niacin Reference Standard.

Standard Niacin Stock Solution II—To 100.0 ml. of *Stock Solution I*, add sufficient water to make 1000.0 ml. Store under toluene in a refrigerator. Each 1.0 ml. represents 10 mcg. of NF Niacin Reference Standard.

Standard Niacin Solution—Dilute a suitable volume of *Stock Solution II* with water to such a measured volume so that after incubation as described in the *Assay Procedure* the transmittance of the 5.0 ml. level of *Standard Niacin Solution* is equivalent to that of a dried cell weight of not less than 1.25 mg., when the inoculated blank is set at 100 percent transmittance. This concentration is usually between 10 and 40 mcg. of niacin per ml. Prepare a fresh *Standard Niacin Solution* for each assay.

Basal Medium Stock Solution

Acid-hydrolyzed Casein Solution	25 ml.
Cystine-Tryptophane Solution	25 ml.
Dextrose Anhydrous	10 g.
Sodium Acetate Anhydrous	5 g.
Adenine-Guanine-Uracil Solution	5 ml.
Riboflavin-Thiamine-Biotin Solution	5 ml.
Aminobenzoic Acid-Calcium Pantothenate-Pyridoxine Solution	5 ml.
Salt Solution A	5 ml.
Salt Solution B	5 ml.

Dissolve the anhydrous dextrose and sodium acetate in the solutions previously mixed, and adjust to a pH of 6.8 with sodium hydroxide T.S. Finally add water to make 250 ml.

Acid-hydrolyzed Casein Solution—Mix 100 g. of vitamin-free casein with 500 ml. of constant-boiling hydrochloric acid (approximately 20 percent HCl) and reflux the mixture for 24 hours. Remove the hydrochloric acid from the mixture by distillation under reduced pressure until a thick paste remains. Redissolve the resulting paste in water, adjust the solution to a pH of 3.5 (±0.1) with sodium hydroxide T.S., and add water to make 1000 ml. Add 20 g. of activated charcoal, stir for 1 hour, and filter. Repeat the treatment with activated charcoal if the filtrate does not appear straw colored to colorless. Store under toluene in a refrigerator. Filter the solution if a precipitate forms upon storage.

Cystine-Tryptophane Solution—Suspend 4.0 g. of *l*-cystine and 1.0 g. of *l*-tryptophane (or 2.0 g. of *dl*-tryptophane) in 700 to 800 ml. of water, heat to 70° to 80°, and add 20 percent hydrochloric acid, dropwise, with stirring, until the solids are dissolved. Cool and add water to make 1000 ml. Store under toluene in a refrigerator at a temperature not below 10°.

Adenine-Guanine-Uracil Solution—Dissolve 100 mg. each of adenine sulfate, guanine hydrochloride, and uracil, with the aid of heat, in 5.0 ml. of 20 percent hydrochloric acid, cool, and add water to make 100 ml. Store under toluene in a refrigerator.

Riboflavin-Thiamine Hydrochloride-Biotin Solution—Prepare a solution containing, in each ml., 20 mcg. of riboflavin, 10 mcg. of thiamine hydrochloride, and 0.04 mcg. of biotin by dissolving crystalline riboflavin, crystalline thiamine hydrochloride and crystalline biotin (free acid) in 0.02 *N* acetic acid. Store, protected from light, under toluene in a refrigerator.

Aminobenzoic Acid-Calcium Pantothenate-Pyridoxine Hydrochloride Solution—Prepare a solution in neutral 25 percent alcohol to contain 10 mcg. of aminobenzoic acid, 20 mcg. of calcium pantothenate, and 40 mcg. of pyridoxine hydrochloride in each ml. Store in a refrigerator.

Salt Solution A—Dissolve 25 g. of monobasic potassium phosphate and 25 g. of dibasic potassium phosphate in water to make 500 ml. Add 5 drops of hydrochloric acid and store under toluene.

Salt Solution B—Dissolve 10 g. of magnesium sulfate, 500 mg. of sodium chloride, 500 mg. of ferrous sulfate, and 500 mg. of manganese sulfate in water to make 500 ml. Add 5 drops of hydrochloric acid and store under toluene.

Stock Culture of Lactobacillus plantarum—Dissolve 2.0 g. of water-soluble yeast extract in 100 ml. of water, add 500 mg. of anhydrous dextrose, 500 mg. of anhydrous sodium acetate and 1.5 g. of agar, and heat the mixture with stirring, on a steam bath, until the agar dissolves. Add approximately 10-ml. portions of the hot solution to test tubes, plug the tubes with cotton, sterilize for 15 minutes in an autoclave at 121° to 123° and allow tubes to cool in an upright position. Prepare stab cultures in 3 or more of the tubes, using a pure culture of *Lactobacillus plantarum*,* incubating for 16 to 24 hours at any selected temperature between 30° and 37°, but held constant to within ±0.5°, and finally store in a refrigerator. Prepare a fresh stab of the stock culture every week and do not use for inoculum if the culture is more than 1 week old.

Culture Medium—To each of a series of test tubes containing 5.0 ml. of the *Basal Medium Stock Solution* add 5.0 ml. of water containing 1.0 mcg. of niacin. Plug the tubes with cotton, sterilize for 15 minutes in an autoclave at 121° to 123°, and cool.

Inoculum—Make a transfer of cells from the stock culture of *Lactobacillus plantarum* to a sterile tube containing 10 ml. of culture medium. Incubate this culture for 16 to 24 hours at any selected temperature between 30° and 37°, but held constant to within ±0.5°. The cell suspension so obtained is the inoculum.

Calibration of the Spectrophotometer—Add aseptically 1 ml. of *Inoculum* to approximately 300 ml. of *Culture Medium* containing 1 ml. of *Standard Niacin Solution*. Incubate the inoculated medium for the same period and at the same temperature to be employed in the *Assay Procedure*.

Following the incubation period, centrifuge, and wash the cells three times with approximately 50-ml. portions of saline T.S., and then resuspend the cells in about 25 ml. of the saline solution.

Dry to constant weight a 10-ml. portion, accurately measured, using a steam bath and completing the drying under vacuum at 100°, and calculate the dry weight of the cells, in mg. per ml., corrected for the amount of sodium chloride present.

Dilute a second portion, accurately measured, of the saline cell suspension with the saline solution so that each ml. contains a known quantity of cells equivalent to 0.5 mg. on a dried basis. To test tubes add, in triplicate, 0.5 ml., 1.0 ml., 1.5 ml., 2.0 ml., 2.5 ml., 3.0 ml., 4.0 ml., and 5.0 ml., respectively, of this diluted cell suspension and 5.0 ml. of *Basal Medium Stock Solution*, and make the volume in each tube to 10.0 ml. with saline solution. Using as the blanks three similar tubes containing no cell suspension, measure the light transmittance of each tube under the same conditions to be employed in the assay. Plot the observations as the ordinate on cross-section paper against the cell content, expressed as mg. of dry weight, as the abscissa.

Repeat this procedure at least twice for the spectrophotometer to be used in the assay. Draw the composite curve best representing the three or more individual curves relating transmittance to cell density for the spectrophotometer under the conditions of the assay.

Assay Procedure—Prepare standard niacin tubes as follows: To duplicate test tubes, add 0.0 ml., 0.5 ml., 1.0 ml., 1.5 ml., 2.0 ml., 2.5 ml., 3.0 ml., 3.5 ml., 4.0 ml., 4.5 ml., and 5.0 ml., respectively, of the *Standard Niacin Solution*. To each tube add 5.0 ml. of *Basal Medium Stock Solution* and water to make 10.0 ml.

Prepare tubes containing the material to be assayed as follows: To duplicate test tubes add, respectively, 1.0 ml., 2.0 ml., 3.0 ml., and 4.0 ml. of the test solution of the material to be assayed. To each tube add 5.0 ml. of *Basal Medium Stock Solution* and water to make 10.0 ml. After mixing, plug the tubes with cotton or cover with caps, and sterilize in an autoclave at 121° to 123°. (Overheating the assay tubes may produce unsatisfactory results.) Cool, aseptically inoculate each tube with 1 drop of inoculum, and incubate for 16 to 24 hours at any selected temperature between 30° and 37°, but held constant to within ±0.5°. Contamination of the assay tubes with any foreign organism invalidates the assay.

Determine the transmittance of the tubes in the following manner. Mix the contents of each tube, to which 1 drop of a suitable antifoam agent solution may be added, and transfer to an optical container. After agitating its contents, place the container in a spectrophotometer that has been set at a specific wavelength between 540 mμ and 660 mμ, and read the transmittance when a steady state is reached. This steady state is observed a few seconds after agitation when the reading remains constant for 30 seconds or more. Allow approximately the same time interval for the reading on each tube.

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* Pure cultures of *Lactobacillus plantarum* may be obtained, as number 8014, from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD 20852.

With the transmittance set at 1.00 for the uninoculated blank, read the transmittance of the inoculated blank. If this transmittance reading corresponds to a dried cell weight greater than 0.6 mg. per tube, or if there is evidence of contamination with a foreign microorganism, disregard the results of the assay.

Then with the transmittance set at 1.00 for the inoculated blank, read the transmittance for each of the remaining tubes. Disregard the results of the assay if the difference between the transmittance observed at the highest level of the standard and that of the inoculated blank is less than the difference corresponding to a dried cell weight of 1.25 mg. per tube.

Calculation—Prepare a standard curve of the niacin standard transmittances for each level of *Standard Niacin Solution* plotted against mcg. of niacin contained in the respective tubes. From this standard curve, determine by interpolation the niacin content of the test solution in each tube. Disregard transmittance values equivalent to less than 0.5 ml. or more than 4.5 ml. of *Standard Niacin Solution.* The niacin content of the test material is calculated from the average values obtained from not less than 6 tubes that do not vary by more than ±10 percent from the average. If the transmittance of less than 6 tubes containing the test solution are within the range of the 0.5-ml. to 4.5-ml. levels of the niacin standard tubes, the data are insufficient to permit calculation of the concentration of niacin in the test material. Transmittance values of inoculated blank exceeding readings corresponding to dried cell weights of more than 600 mcg. per tube indicate the presence of an excessive amount of niacin in the *Basal Medium Stock Solution* and invalidate the assay.

Multiply the values obtained by 0.992 if the results are to be expressed as niacinamide.

NITROGEN DETERMINATION

Some alkaloids and other nitrogen-containing organic compounds fail to yield all of their nitrogen upon digestion with sulfuric acid; therefore this method cannot be used for the determination of nitrogen in all organic compounds.

Method I

Nitrates and Nitrites Absent—Place about 1 g. of the substance, accurately weighed, in a 500-ml. Kjeldahl flask of hard glass. The material to be tested, if solid or semi-solid, may be wrapped in a sheet of nitrogen-free filter paper for convenience in transferring it to the flask. Add 10 g. of powdered potassium sulfate or anhydrous sodium sulfate, 500 mg. of powdered cupric sulfate, and 20 ml. of sulfuric acid. Incline the flask at an angle of about 45°, and gently heat the mixture, keeping the temperature below the boiling point until frothing has ceased. Increase the heat until the acid boils briskly, and continue the heating until the solution has been clear green in color or almost colorless for 30 minutes. Allow to cool, add 150 ml. of water, mix the contents of the flask, and again cool. Add cautiously 100 ml. of sodium hydroxide solution (4 in 10), in such manner as to cause the solution to flow down the inner side of the flask to form a layer under the acid solution. Add a few pieces of granulated zinc, and connect the flask, by means of a Kjeldahl connecting bulb, with a condenser, the delivery tube from which dips beneath the surface of 50 ml. of boric acid solution (1 in 25) contained in a conical flask or a wide-mouth bottle of about 500-ml. capacity. Mix the contents of the Kjeldahl flask by gentle rotation, and distil until about two-thirds of the contents of the flask has distilled over. Add about 3 drops of methyl red-methylene blue T.S. to the contents of the receiving vessel, and determine the ammonia by titration with 0.5 *N* sulfuric acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.5 *N* acid is equivalent to 7.003 mg. of nitrogen.

When the nitrogen content of the substance is known to be low, the 0.5 *N* sulfuric acid may be replaced by 0.1 *N* acid. Each ml. of 0.1 *N* sulfuric acid is equivalent to 1.401 mg. of nitrogen.

Nitrates and Nitrites Present—Place a quantity of the substance, accurately weighed, corresponding to about 150 mg. of nitrogen, in a 500-ml. Kjeldahl flask of hard glass, and add 25 ml. of sulfuric acid in which 1 g. of salicylic acid previously has been dissolved. Mix the contents of the flask, and allow the mixture to stand for 30 minutes with frequent shaking. To the mixture add 5 g. of powdered sodium thiosulfate, again mix, then add 500 mg. of powdered cupric sulfate, and proceed as directed under *Nitrates and Nitrites Absent,* beginning with "Incline the flask at an angle of about 45°. . . ."

When the nitrogen content of the substance is known to exceed 10 percent, 500 mg. to 1.0 g. of benzoic acid may be added, prior to digestion, to facilitate the decomposition of the substance.

Method II

Apparatus—Select a unit of the general type known as a semimicro Kjeldahl apparatus by which the nitrogen is first liberated by acid digestion and then transferred quantitatively to the titration vessel by steam distillation.

Procedure—Place an accurately weighed or measured quantity of the material, equivalent to 2 to 3 mg. of nitrogen, in the digestion flask of the apparatus. Add 1 g. of a powdered mixture of 10 parts of potassium sulfate and 1 part of cupric sulfate, and wash down any adhering material from the neck of the flask with a fine jet of water. Add 7 ml. of sulfuric acid, allowing it to rinse down the wall of the flask, then, while swirling the flask, add 1 ml. of 30 percent hydrogen peroxide cautiously down the side of the flask. (Do not add hydrogen peroxide during the digestion.)

Heat the flask over a free flame or an electric heater until the solution has a clear blue color and the sides of the flask are free from carbonaceous material. Cautiously add to the digestion mixture 20 ml. of water, cool the solution, and arrange for steam distillation. Add through a funnel 30 ml. of sodium hydroxide solution (4 in 10), rinse the funnel with 10 ml. of water, tightly close the apparatus, and begin the distillation with steam at once. Receive the distillate in 15 ml. of boric acid solution (1 in 25), to which has been added 3 drops of methyl red-methylene blue T.S., and sufficient water to cover the end of the condensing tube. Continue the distillation until the distillate measures 80 to 100 ml. Remove the absorption flask, rinse the end of the condensing tube with a small quantity of water, and titrate the distillate with 0.01 *N* sulfuric acid. Perform a blank determination, and make any necessary correction. Each ml. of 0.01 *N* acid is equivalent to 140.1 mcg. of nitrogen.

When a quantity of material containing more than 2 to 3 mg. of nitrogen is taken, 0.02 *N* or 0.1 *N* sulfuric acid may be employed, provided that at least 15 ml. is required for the titration. If the total dry weight of material taken is greater than 100 mg. increase proportionately the quantities of sulfuric acid and sodium hydroxide.

OPTICAL ROTATION

Many drugs, in a pure state or in solution, are optically active in the sense that they cause incident polarized light to emerge in a plane forming a measurable angle with the plane of the incident light. Where this effect is large enough for precise measurement, it may serve as the basis for an assay or an identity test. In this connection, the optical rotation is expressed in degrees, as either *angular rotation* (observed) or *specific rotation* (calculated with reference to the specific concentration of 1 g. of solute in 1 ml. of solution, measured under stated conditions).

Specific rotation usually is expressed by the term, $[\alpha]_x^t$, in which t represents, in degrees centigrade (Celsius), the temperature at which the rotation is determined, and x represents the characteristic spectral line or wavelength of the light used. Unless otherwise specified, the values cited in this National Formulary relate to the D line of sodium. Spectral lines most frequently employed are the D line of sodium (doublet at 589.0 mμ and 589.6 mμ) and the yellow-green line of mercury at 546.1 mμ. The specific gravity and the rotatory power may vary appreciably with the temperature.

The accuracy and precision of optical rotatory measurements will be increased if they are carried out with due regard for the following general considerations.

The instrument itself must be in good condition. Optical elements must be brilliantly clean and in exact alignment. The match point should lie close to the normal zero mark. The light source should be rigidly set and well aligned with respect to the optical bench. It should be supplemented by a filtering system capable of transmitting light of a sufficiently monochromatic nature. Precision polarimeters generally are designed to accommodate interchangeable disks to isolate the D line from sodium light or the 546.1 mμ line from the mercury spectrum. With polarimeters not thus designed, cells containing suitably colored liquids may be employed as filters [see *Technique of Organic Chemistry*, A. Weissberger, Vol. I, Part III, 3rd ed. (1960), Interscience Publishers, Inc., New York, N. Y.].

Special attention should be paid to temperature control of the solution and of the polarimeter. Observations should be accurate and reproducible to the extent that differences between replicates, or between observed and true values of rotation (the latter value having been established by calibration of the polarimeter scale with suitable standards), calculated in terms of either *Specific rotation* or *Angular rotation*, whichever is appropriate, shall not exceed one-fourth of the range given in the individual monograph for the rotation of the article being tested. Generally, a polarimeter accurate to 0.05° of angular rotation, and capable of being read with the same precision, suffices for National Formulary purposes; in some cases, a polarimeter accurate to 0.01°, or less, of angular rotation, and read with comparable precision, may be required.

Polarimeter tubes should be filled in such a way as to avoid creating or leaving air bubbles which interfere with the passage of the beam of light. Interference from bubbles is minimized with tubes in which the bore is expanded at one end. However, with tubes of uniform bore, such as semimicro or micro tubes, care is required for proper filling.

In closing tubes having removable end-plates fitted with gaskets and caps, the latter should be tightened only enough to ensure a leak-proof seal between the end-plate and the body of the tube. Excessive pressure on the end-plate may set up strains that result in interference with the measurement. In determining the specific rotation of a substance of low rotatory power, it is desirable to loosen the caps and tighten them again between successive readings in the measurement of both the rotation and the zero point. Differences arising from end-plate strain thus generally will be revealed and appropriate adjustments to eliminate the cause may be made.

Procedure—Where the substance is a liquid, adjust its temperature to 25°, and transfer it to the polarimeter tube. Proceed as directed below, beginning with "Make at least five readings," but carry out the blank determination on the empty, dry tube.

Where the substance is a solid, weigh a suitable portion and transfer it to a volumetric flask by means of water, or other solvent if specified, reserving a portion of the solvent for the blank determination. Add enough solvent to bring the meniscus close to but still below the mark, and adjust the flask contents to 25°, as by suspending the flask in a constant temperature bath. Add solvent to the mark, and mix. Transfer the solution to the polarimeter tube within 30 minutes from the time the substance was dissolved, taking care to standardize the elapsed time in the case of substances known to undergo racemization or mutarotation. During the elapsed time interval maintain the solution at 25°.

Make at least five readings, at 25°, of the observed rotation. Substitute the reserved solvent for the solution, and make an equal number of readings on it. The zero correction is the average of the blank readings, and is subtracted from the average observed rotation if the two figures are of the same sign, or added if they are opposite in sign, to give the corrected observed rotation (+ indicates dextrorotation; − indicates levorotation).

Calculation—Calculate the specific rotation of a liquid substance, or of a solid in solution, by application of one of the following formulas: (I) For liquid substances, $[\alpha]_x^t = (a/ld)$; (II) For solutions of solids, $[\alpha]_x^t = (100a/lpd) = (100a/lc)$; in which a is the corrected observed rotation, in degrees, at temperature t; l is the length of the polarimeter tube in decimeters; d is the specific gravity of the liquid or solution at the temperature of observation; p is the concentration of the solution expressed as the number of g. of substance in 100 g. of solution; and c is the concentration of the solution expressed as the number of g. of substance in 100 ml. of solution.

OXYGEN FLASK COMBUSTION

The caution statement given under *Procedure* covers minimum safety precautions only, and serves to emphasize the need for exceptional care throughout.

Apparatus—The apparatus consists of a thick-walled, conical, deeply lipped or cupped 500-ml. flask, into the stopper of which is fused a platinum wire sample holder usually made of heavy-gauge platinum wire and a piece of welded platinum gauze measuring about 1.5 × 2 cm.

Procedure—[Caution—The analyst should wear safety glasses and use a suitable safety shield between himself and the apparatus. The flask must be scrupulously clean and free from even traces of organic solvents.] Weigh the substance, if a solid, on a piece of halide-free filter paper measuring about 4 cm. square, and fold the paper to enclose it. Liquid substances may be weighed in tared gelatin capsules. [Note—Gelatin capsules may contain significant amounts of combined halide or sulfur. If such capsules are used, perform a blank determination and make any necessary correction.] Place the sample, together with a filter paper fuse-strip, in the platinum gauze sample holder. Place the absorbing liquid specified in the individual monograph in the flask, moisten the joint of the stopper with water, and flush the air from the flask with a stream of rapidly flowing oxygen, swirling the liquid to favor its taking up oxygen. Ignite the fuse-strip by suitable means. If the strip is ignited outside the flask, immediately plunge the sample holder into the flask, invert the flask so that the absorption solution makes a seal around the stopper, and hold the stopper firmly in place. If the ignition is carried out in a closed system, the inversion of the flask may be omitted. After combustion is complete, shake the flask vigorously, and allow to stand for not less than 10 minutes with intermittent shaking. Then proceed as directed in the individual monograph.

pH DETERMINATION

Definitions—For National Formulary purposes, pH is defined as the value given by a suitable, properly standardized, potentiometric instrument (pH meter) capable of reproducing pH values to 0.02 pH units using an indicator electrode sensitive to hydrogen ion activity, most commonly the glass electrode, and an appropriate reference electrode, e.g. a silver-silver chloride or calomel electrode. The instrument should be capable of sensing the potential across the electrode pair and, for pH standardization purposes, applying an adjustable potential to the circuit by manipulation of "standardization", "zero", "asymmetry", or "calibration" control, and should be able to control the change in millivolts per unit change in pH reading through a "temperature" or "slope" control. Measurements should be made at 25 ± 2°, unless otherwise specified in the individual monograph or procedure.

The pH scale is defined by the equation $\mathrm{pH} = \mathrm{pHs} + (E - E\mathrm{s})/k$, in which E and Es are the measured potentials when the galvanic cell contains the solution under test, represented by pH, and the appropriate Buffer Solution for Standardization, represented by pHs, respectively. The value of k is the change in potential per unit change in pH and is theoretically $0.05916 + 0.000198(t - 25°)$ volts at any temperature t. This operational pH scale is established by assigning rounded pH values to the *molar* solutions of the Buffer Solutions for Standardization from the equivalent National Bureau of Standards *molal* solutions.

It should be emphasized that the definitions of pH, the pH scale, and the values assigned to the Buffer Solutions for Standardization are for the purpose of establishing a practical, operational system so that results may be compared between laboratories. The pH values measured in this fashion do not correspond exactly to those obtained by the classical definition, $\mathrm{pH} = -\log [\mathrm{H^+(aq)}]$. So long as the solution being measured is sufficiently similar in composition to the buffer used for standardization, the operational pH corresponds fairly closely to the theoretical pH. No claim is made as to the suitability of the system for measuring hydrogen ion activity or concentration; however, the values obtained will be closely related to the activity of the hydrogen ion in aqueous solutions.

When a pH meter is standardized by use of an aqueous buffer and then used to measure the "pH" of a nonaqueous solution or suspension, the ionization constant of the acid or base, the dielectric constant of the medium, the liquid-junction potential (which may give rise to errors of approximately 1 pH unit), and the hydrogen-ion response of the glass electrode are all changed. For these reasons, the values so obtained on solutions which are only partially aqueous in character can be regarded only as apparent pH values. On the other hand, studies of the response of some hydrogen ion-sensitive electrodes, including the glass electrode, in some nonaqueous solutions have indicated that acidities may be accurately measured when proper electrode use and instrumental standardization are respected.

Instrumental Standardization and Determination of pH—Buffer Solutions for Standardization are to be prepared according to the directions found in the table which follows. Buffer salts of requisite purity can be obtained from the National Bureau of Standards, Washington, D.C. Solutions may be stored in bottles of Type I glass. Fresh solutions should be prepared at intervals not to exceed 3 months. The table on page 905 indicates the pH of the buffer solutions as a function of temperature.

Buffer Solutions for Standardization

Potassium Tetraoxalate, 0.05 *M*—Dissolve 12.61 g. of $\mathrm{KH_3(C_2O_4)_2.2H_2O}$ in sufficient water to make 1000 ml.

Potassium Biphthalate, 0.05 *M*—Dissolve 10.21 g. of $\mathrm{KHC_8H_4O_4}$, previously dried at 110° for 1 hour, in sufficient water to make 1000 ml.

Equimolar Phosphate, 0.05 *M*—Dissolve 3.533 g. of $\mathrm{Na_2HPO_4}$ and 3.388 g. of $\mathrm{KH_2PO_4}$, each previously dried at 120° for 2 hours, in sufficient water to make 1000 ml.

Sodium Tetraborate, 0.01 *M*—Dissolve 3.80 g. of $\mathrm{Na_2B_4O_7.10H_2O}$ in sufficient water to make 1000 ml. Protect from absorption of carbon dioxide.

Calcium Hydroxide, saturated at 25°—Shake an excess of calcium hydroxide with water, decant at 25° before use. Protect from absorption of carbon dioxide.

Because of variations in the nature and operation of the available pH meters, it is not practicable to give detailed universally applicable directions for the potentiometric determinations of pH. The general principles to be followed in carrying out the instructions provided for each instrument by its manufacturer are set forth in the following paragraphs. Examine the electrodes and, if present, the salt bridge prior to use. If necessary, replenish the salt bridge solution and observe other precautions indicated by the instrument or electrode manufacturer.

To standardize the pH meter select two *Buffer Solutions for Standardization* whose difference in pH does not exceed 4 units and such that the expected pH of the sample falls between them. Fill the cell with one of the *Buffer Solutions for Standardization* at the temperature at which the sample is to be measured. Set the "temperature" control at the temperature of the solution and adjust the calibration control to make the observed pH value identical with that tabulated. Rinse the electrodes and cell with several portions of the second *Buffer Solution for Standardization* then fill the cell with it, at the same temperature as the sample to be measured. The second buffer solution pH should be within ±0.02 pH units of the accepted nominal value. If a larger deviation is noted, the electrodes may be faulty and should be examined and, if necessary, replaced. When the system is functioning satisfactorily, rinse the electrodes and cell several times with a few portions of the sample, fill the cell with the sample and read the pH value. Use carbon dioxide-free water (see page 11) for solution or dilution of sample in pH determinations.

PHARMACEUTICAL PREPARATIONS

Dosage forms are provided for most of the official drug substances, but the processes for the preparation of many of them are, in general, outside the scope of the National Formulary. This section gives general definitions of various dosage forms and presents the general principles involved in the manufacture of some of them, particularly on a small scale. Other information that is given bears on the use of official substances in extemporaneous compounding of dosage forms not officially recognized.

Aerosols

Aerosols are pressurized dosage forms containing one or more active ingredients which upon actuation give a fine dispersion of liquid and/or solid materials in a gaseous medium. Pressure is supplied to the system by means of one or more propellants. The term aerosol is not restricted to true colloidal systems since dispersions ranging from a few hundredths of a μ to several hundred μ are obtained. For inhalation therapy, the particle size of the delivered medication must be carefully controlled and should be under 10 μ.

The basic components of an aerosol system are the container, propellant, concentrate containing the active ingredients, valve, and actuator. Depending upon the formulation, various suspending or emulsifying agents and/or cosolvents may also be present. Variations among these components are extremely numerous, and different combinations may be utilized to achieve desirable product characteristics. Such characteristics include proper particle size and homogeneity of the dispersed phase, wetness, dryness, uniformity, force, shape, and temperature of the spray, area covered, dosage delivered, and delivery rate.

Aerosols may consist of two-phase (gas and liquid) or three-phase (gas, liquid, and solid or liquid) systems. In some cases it is possible to dissolve certain formulations in the propellant which results in a two-phase aerosol. However, in most instances, it is necessary to use a cosolvent to aid in achieving solution, since many of the commonly used propellants have relatively low solvent power. Where solution is not possible or practical, the formulation may be emulsified or suspended in the propellant which results in a three-phase system. To avoid coalescence or sediment compaction in three-phase aerosols, suitable adjustments in propellant density are made and appropriate emulsifying or suspending agents are used.

Aerosols are available for a variety of therapeutic uses. For topical application, nonmetered spray dosage forms are widely used. Metered dosage forms delivering a single measured dose of medication upon each actuation are available for oral or nasal inhalation to provide the desired systemic and local effects.

Containers—Aerosol containers include those made of glass, plastic, or metal, or a combination of these materials. Glass containers must be precisely engineered to provide the maximum in pressure safety and impact resistance. Plastics may be employed to coat glass containers for improved safety characteristics or for metal containers to improve corrosion resistance and enhance stability characteristics. Suitable metals include stainless steel, aluminum, and tinplated steel.

Valves—The primary function of the valve is to regulate the flow of the therapeutic agent and propellant from the container. The spray characteristics of the aerosol are influenced by means of properly sized orifice dimensions, numbers, and location. Valves may provide for continuous spray operation or metered dose delivery. Spray valves may be designed for good space dispersion or surface dispersion characteristics. Special types of valves provide for foam-type extrusions. Vapor tap valves allow a portion of the gas phase to be evacuated along with the liquid or suspension phase to achieve proper spray properties and to assist in obtaining desired pressure equilibrium characteristics as the aerosol is used. Materials used for the manufacture of valves should be inert toward the formulations used and may be plastic, rubber, aluminum, or stainless steel. Metered dose valves must deliver an accurate dose within specified tolerances (see page 771).

Propellants—The propellant supplies the necessary pressure within an aerosol system to expel material from the container and, in combination with other components, to convert the material into the desired physical form. Propellants may be broadly classified as liquified or compressed gases with vapor pressures generally exceeding atmospheric pressure. Propellants under this definition include various hydrocarbons, especially fluorochloro derivatives of methane and ethane, low molecular weight hydrocarbons such as the butanes and pentanes, and compressed gases such as carbon dioxide, nitrogen, and nitrous oxide. Mixtures of propellants are frequently used to obtain desirable pressure, delivery, and spray characteristics. A good propellant system should have the proper vapor pressure characteristics consistent with the other aerosol components. Good solvent power is desirable but not a necessary requirement.

Actuators—An actuator is the fitting attached to an aerosol valve stem which, under depression or movement, opens the valve, operates the aerosol, and directs the spray to the desired area. The actuator usually indicates the direction of spray and protects the hand or finger from the refrigerant effects of the propellant. Actuators incorporate a spray orifice which may vary widely in dimension. The size of this orifice, the expansion chamber design, and the nature of the propellant and formulation influence the characteristics of the aerosolized material.

Cosolvents—Cosolvents are those substances used to enhance the solubility of a formulation in a propellant system. In order to prepare a single-phase liquid system, these cosolvents must be soluble in the propellant. Alcohol is widely used since it is miscible with most propellant systems and has good dissolving power for many formulation materials. Other substances, such as propylene glycol, polypropylene glycol, polyethylene glycols, and diethylene glycol monomethyl ether, or its derivatives, may also be used as cosolvents.

Manufacture—Aerosols are usually prepared by one of two general processes. In the "cold-fill" process, the concentrate (generally cooled to below 0°) and the refrigerated propellant are measured into open containers (usually chilled). The valve-actuator assembly is then crimped onto the container to form a pressure-tight seal. During the interval between propellant addition and crimping, sufficient volatilization of propellant occurs to displace air from the container. In the "pressure-fill" method, the concentrate is placed in the container, and the propellant is either forced under pressure through the valve orifice after the valve is sealed, or the propellant is allowed to flow under the valve cup and then the valve assembly is sealed ("under-the-cap" filling). In both cases of the "pressure-fill" method, provisions must be made for evacuation of air by means of vacuum or displacement with a small amount of propellant. Manufacturing process controls usually include monitoring of proper formulation and propellant fill weight, and pressure testing and leak testing of the finished aerosol.

Labeling—Medicinal aerosols should at least contain the following warning information on the label as in accordance with appropriate regulations:

> Warning: Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 130°F. Keep out of the reach of children.

Aromatic Waters

Aromatic waters are saturated solutions (unless otherwise specified) of volatile oils or other aromatic or volatile substances in purified water. Their odors and tastes are similar, respectively, to those of the drugs or volatile substances from which they are prepared, and they are free from empyreumatic and other foreign odors.

Aromatic waters may be prepared by one of the following processes:

(**a**) **Solution**—

The Volatile Oil, or Other Specified Volatile Substance	2 ml. or 2 g.
Purified Water, a sufficient quantity,	
To make	1000 ml.

Shake the volatile substance (suitably comminuted if a solid) with 1000 ml. of purified water in a capacious bottle, and repeat the shaking several times during a period of about 15 minutes. Set the mixture aside for 12 hours or longer, filter through wetted filter paper, and pass enough purified water through the filter to make the product measure 1000 ml.

Alternative Solution Method—Thoroughly incorporate the volatile oil (or the suitably comminuted volatile solid) with 15 g. of talc or with a sufficient quantity of purified siliceous earth or pulped filter paper. Add 1000 ml. of purified water, and thoroughly agitate the mixture several times during 10 minutes. Then filter the mixture, returning the first portions, if necessary, to obtain a clear filtrate, and add enough purified water through the filter to make the product measure 1000 ml.

(**b**) **Distillation**—Place the odoriferous portion of the plant or drug from which the aromatic water is to be prepared in a suitable still with sufficient purified water, and distil most of the water, carefully avoiding the development of empyreumatic odors through the charring or scorching of the substances. Separate the excess of oil, and preserve or use the clear water portion, filtering if necessary.

Packaging and Storage—Protect aromatic waters from intense light and excessive heat.

Capsules

Capsules are solid dosage forms in which the drug is enclosed in either a hard or a soft, soluble container or "shell" of a suitable form of gelatin. Capsule sizes range from No. 5, the smallest, to No. 000, which is the largest except for the veterinary sizes. Factory-filled hard capsules are often of distinctive color and shape or are otherwise marked to identify them with the maker. In extemporaneous prescription practice, the use of capsules permits a latitude of choice in prescribing either a single drug or a combination of drugs at the precise dosage level considered best for the individual patient by his physician.

Mixtures that tend to liquefy may be dispensed in capsules if an absorbant such as magnesium carbonate or another suitable substance is used. Potent drugs given in small doses are usually mixed with an inert diluent before filling into capsules. When two mutually incompatible drugs are prescribed together, it is sometimes possible to place one in a small capsule and then enclose it with the second drug in a larger capsule.

Soft gelatin capsules generally require large-scale production methods. The gelatin shell is somewhat thicker than that of hard capsules and is plasticized by the addition of some polyol, such as glycerin or sorbitol. This dosage form is used for oils and oil solutions as well as powdered drugs, the latter being encapsulated dry or as a suspension in oil. Water is excluded because of its effect on the gelatin shell.

Capsules that have been treated to resist solution in the gastric fluid should meet the requirements for disintegration of enteric-coated tablets (see page 878).

Capsules should be dispensed in tight containers to prevent the absorption of moisture. Finished capsules are usually treated to prevent the surface growth of fungi.

Collyria—See *Ophthalmic Solutions*

Creams

Creams are semisolid emulsions of either the oil-in-water or the water-in-oil type. They are ordinarily used topically and so may be classed broadly as water-containing ointments, *e.g.*, *Hydrophilic Ointment*. (See also *Water-removable Bases* under *Ointments*, page 832.)

Elixirs

Elixirs are clear, sweetened, hydroalcoholic liquids intended for oral use. They contain flavoring substances and, in the case of medicated elixirs, active medicinal agents. Their primary solvents are alcohol and water, with glycerin, sorbitol, and syrup sometimes used as additional solvents and/or sweetening agents. They are prepared by simple solution or admixture of the several ingredients.

They are used either as vehicles (*e.g.*, *Iso-Alcoholic Elixir*) or for the therapeutic effect of the medicinal substance that they contain (*e.g.*, *Terpin Hydrate and Codeine Elixir* and *Amobarbital Elixir*).

A high alcohol content may increase the solvent power for some drugs. On the other hand, it is a disadvantage with bromides and other saline drugs in that it accentuates their saline taste.

Emulsions

An emulsion is a dispersed system in which one liquid, termed the "dispersed" or "internal" phase, is distributed in small globules throughout the body of a second liquid, termed the "dispersion medium" or "external" phase. Where oil is the dispersed phase and an aqueous solution is the dispersion medium, the emulsion is said to be an *oil-in-water* (o/w) emulsion. Such an emulsion usually is miscible with water. Where water or an aqueous solution is the dispersed phase, and oil or oleaginous material is the dispersion medium, the emulsion is described as a *water-in-oil* (w/o) emulsion, and usually is miscible with oil.

Emulsions are stabilized by suitable emulsifying agents or surfactants that tend to lower the interfacial tension between oil and water in a way that makes fairly stable dispersion possible. The solubility characteristics of the emulsifying agent very largely control the type of emulsion produced, although other factors, such as phase-volume ratio, also are involved. Thus, gelatin and polysorbate 80, which are water-soluble, make possible the dispersion of oil in water, while the oil-soluble surfactants, cholesterol and stearyl alcohol, which are found in *Hydrophilic Petrolatum*, make it possible to incorporate water and thereby form a semisolid, water-in-oil emulsion.

An oil is best prepared for oral administration by first emulsifying it in a flavored, sweetened, aqueous medium. Only oil-in-water emulsions are suitable for oral use, since they are water-miscible and thus their "oiliness" is masked. A number of emulsifying agents, such as acacia and gelatin, make such emulsions easy to prepare.

In preparing National Formulary emulsions, methods of emulsification other than those described in the several monographs may be used, and the quantity of acacia may be reduced, or it may be replaced in whole or in part with gelatin, tragacanth, agar, or mixtures of these.

Gelatin meeting USP specifications but particularly suited for the preparation of emulsions is available in two types, known as Types A and B, which are used under different circumstances.

Type A gelatin is prepared from acid-treated precursors and is used at a pH of about 3.2. It is preferred if no other emulsifying agents are used. It is incompatible with anionic emulsifying agents such as the vegetable gums. For its use in the extemporaneous preparation of emulsions, the following procedure is recommended:

Gelatin (Type A)........	8.0 g.
Tartaric Acid...........	0.6 g.
Flavor as desired	
Alcohol.................	60 ml.
Oil.....................	500 ml.
Purified Water, to make...	1000 ml.

Add the gelatin and the tartaric acid to about 300 ml. of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98°, and maintain this temperature for about 20 minutes. Cool to 50°, and add the flavor, the alcohol, and sufficient purified water to make 500 ml. Add the oil, agitate the mixture thoroughly, and pass it through a homogenizer or a colloid mill until the oil is completely and uniformly dispersed.

This emulsion cannot be prepared by trituration or by use of the usual stirring devices.

Type B gelatin is prepared from alkali-treated precursors and is used at a pH of about 8.0. It may be used with or without other anionic emulsifying agents. It is incompatible with cationic emulsifying agents. For 1000 ml. of an emulsion containing 50 percent of oil, a mixture of 5 g. of Type B gelatin, 2.5 g. of sodium bicarbonate and sufficient tragacanth or agar to provide the required viscosity is used.

For an external product, the decision as to whether an oil-in-water or a water-in-oil emulsion is the better type depends on many factors, such as the nature of the therapeutic agents incorporated, the desirability of an emollient effect, the condition of the skin surface, etc. On the unbroken skin, a water-in-oil emulsion can be applied more evenly since the skin surface is covered with a thin film of sebum and the surface is more readily wetted by oil than by water. Water-soluble antiseptics are more active but also potentially more irritating when incorporated in an oil-in-water emulsion.

Hydrophilic Ointment is an example of an oil-in-water emulsion, while the incorporation of water into *Hydrophilic Petrolatum* produces a water-in-oil emulsion.

Emulsions usually require a preservative, since the aqueous phase is favorable to the growth of microorganisms. A combination of methylparaben and propylparaben is suitable for the purpose. The required concentration of each depends on the nature of the product and the presence or absence of other substances having preservative qualities. Other preservatives, such as benzoic acid, quaternary ammonium compounds, and alcohol, are also available. For internal products, alcohol in a concentration of 12 to 15 percent, based on the volume of the external phase, is often used.

In flavoring emulsions for oral administration, only those flavors known to be suitable for internal use should be added. Furthermore, only minimal amounts of flavors and sweetening agents should be used, since large amounts may cause nausea or gastric distress in the patient.

(See also *Creams; Ointments.*)

Extracts

Extracts are concentrated preparations of vegetable or animal drugs obtained by extracting the active constituents of the respective drugs with suitable menstruums, evaporating all or nearly all of the solvent, and adjusting the residual masses or powders to the prescribed standards.

Extracts are made in three forms: semiliquid or those of syrupy consistency; plastic masses, known as *pilular or solid extracts;* and dry powders, known as *powdered extracts.* Pilular extracts and powdered extracts of any one drug are interchangeable medicinally, but each has its pharmaceutical advantages.

In the manufacture of most extracts, the drugs are extracted by the process of percolation. The rate of flow of percolates, directed under the several monographs, is defined under *Fluidextracts*, page 829. The entire percolates are concentrated by distillation under reduced pressure, with a few exceptions, in order to expose the drug principles to as little heat as possible. If the active principles of a drug are damaged by high temperatures or by prolonged heating, the temperature at which its percolate is concentrated is not to exceed 60° at any stage.

Diluents—Extracts which must be adjusted to prescribed standards may need diluents for that purpose. While in the National Formulary liquid glucose is directed as the diluent for pilular extracts, and starch dried at 100° for powdered extracts, the following additional diluents are permitted: malt extract and/or glycerin or glucose for pilular extracts, and for powdered extracts, sucrose, lactose, powdered glycyrrhiza, magnesium carbonate, magnesium oxide, calcium phosphate, the finely powdered marc remaining after the extraction of the drug, or other inert, nontoxic diluents. Magnesium carbonate and magnesium oxide must not be used in powdered extracts of belladonna and hyoscyamus. The diluent for a powdered extract may be colored with chlorophyll or caramel to produce a color corresponding to the normal color of the extract, but an excess of coloring agent must not be added.

Defatting Extracts—Powdered extracts which are made from drugs that contain a material proportion of inactive oily or fatty matter should have this removed in order to obtain a satisfactory product. Any suitable method for defatting either the drug or the extract may be employed. The following methods for treating the extract are recommended:

Method I—Prepare the extract in the regular manner to the point where, before final adjustment, it is dried with a portion of starch. To this dry powder add solvent hexane (about 300 ml. of hexane for each 100 g. of drug extracted) and stir well several times during 2 hours. Allow to settle, and decant or drain off the excess of liquid. Mix the residue with another (smaller) portion of solvent hexane, stir thoroughly, and separate the excess of hexane. Repeat the washing with a third portion of solvent hexane, then drain the powder, and dry it thoroughly at a temperature not exceeding 70°. Weigh the dried powder, and adjust it to the prescribed quantity or strength.

Method II—To the soft extract obtained by the evaporation of the percolate, add slightly acidified water at a temperature of about 80° in the proportion of about 80 ml. of acidified water to each 100 g. of soft extract or crude drug represented. Stir the mixture thoroughly, and allow it to stand until almost cold. Remove and discard any oily or fatty matter which has risen, then separate and retain the water layer. Treat the undissolved extract residue twice as just described, combine and evaporate the water liquids to a soft extract at a temperature not exceeding 70°. Mix the soft extract thus obtained with a portion of starch, dry the mixture at a temperature not exceeding 70°, and complete the extract in the usual way.

The acidified water suggested above contains about 0.05 percent of HCl or about 0.2 percent of tartaric acid.

Packaging and Storage—Preserve Extracts in tight, light-resistant containers, preferably at a temperature not above 30°, or as directed in the individual monograph.

Fluidextracts

Fluidextracts are liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, and so made that each ml. contains the therapeutic constituents of 1 g. of the standard drug which it represents.

The official fluidextracts are made by the process of percolation, the menstruum to be used being specified in each monograph. Manufacture by the usual process calls for concentration of the more diluted portion of percolate by distillation. This should be done in a vacuum distillation apparatus, the temperature in the still being kept below 60°.

The time of maceration and the rate of flow during percolation are varied for different drugs to compensate for peculiarities in extraction and in some cases to accomplish partial rejection of nonactive constituents. In all cases the maceration and rate of flow are designed to extract completely the medicinally active or important constituents from the specified quantities of drugs: but the time and rate specified may be varied to accomplish this purpose when larger or smaller quantities of drug are being treated.

Usually a cylindrical form of percolator is the best type for making fluidextracts, but for use with drugs which swell considerably in the menstruum a flaring form of percolator may be preferred.

The rate of flow of the percolate is directed in these terms: "percolate slowly," "percolate rapidly," and "percolate at a moderate rate." With reference to the extraction of 1000 g. of drug, "percolate slowly" means a rate not exceeding 1 ml. of percolate per minute; "percolate rapidly" means a rate of 3 to 5 ml. per minute; "percolate at a moderate rate," means a rate of 1 to 3 ml. per minute.

A fluidextract which may deposit sediment may be aged and filtered or the clear portion decanted, provided the resulting clear liquid conforms to the official standards.

The general processes of manufacture directed by the National Formulary are as follows:

Process A—This process is used for preparing fluidextracts, which are made with menstruums of alcohol or of mixtures of alcohol and water, by ordinary percolation.

Carefully mix 1000 g. of the ground drug with a sufficient quantity of the prescribed menstruum to render it evenly and distinctly damp. This usually requires from 600 ml. to 800 ml. of menstruum. Allow the dampened drug to stand for about 15 minutes, then pack it firmly in a suitable percolator, and pour on sufficient menstruum to saturate the drug and leave a stratum above. When the liquid is about to drop from the percolator, close the lower orifice, cover the percolator, and allow the drug to macerate for the prescribed period of time. Then proceed with the percolation at the specified rate, adding fresh menstruum as needed until the drug is practically exhausted of its active principles. Reserve the first 850 ml. of percolate (unless otherwise directed in the formula), recover the alcohol from the percolate subsequently collected, and concentrate the residue to a soft extract at a temperature not exceeding 60°. Dissolve this extract in the reserved percolate, and if no assay is directed, add enough of a mixture of alcohol and water to make the fluidextract measure 1000 ml. and contain the required proportion of C_2H_5OH. Mix thoroughly. If the fluidextract being prepared is to be adjusted to a standard, assay a portion of the reserved percolate in which the soft extract has been dissolved, and dilute the remainder to the volume determined as necessary by calculation from the assay, using a sufficient quantity of an alcohol and water mixture to provide the required proportion of C_2H_5OH. Mix thoroughly.

Process B—This process is used in preparing fluidextracts, portions of the menstruums for which contain, in addition to alcohol or a mixture of alcohol and water, definite quantities of other components such as an acid or glycerin, the two menstruums being successively employed.

Carefully mix 1000 g. of the ground drug with a sufficient quantity of Menstruum I (containing the special ingredient) to render it evenly and distinctly damp. From 600 ml. to 800 ml. of menstruum is usually required. Allow the dampened drug to stand for about 15 minutes, then pack it firmly in a suitable percolator, and pour on the remainder of Menstruum I. When the liquid is about to drop from the percolator, close the lower orifice, cover the percolator, and allow the drug to macerate for the prescribed period of time. Then proceed with the percolation at the specified rate, and when the first menstruum has disappeared from the surface of the drug, use Menstruum II as needed until the drug is exhausted of its active principles. Reserve the first 850 ml. of percolate, recover the alcohol from the percolate subsequently collected, and evaporate the residue to a soft extract at a temperature not exceeding 60°. Dissolve this extract in the reserved percolate, and if no assay is directed, add enough of a mixture of alcohol and water to make the fluidextract measure 1000 ml. and contain the required proportion of C_2H_5OH. Mix thoroughly. If the fluidextract being prepared is to be adjusted to a standard, assay a portion of the reserved percolate in which the soft extract has been dissolved, and dilute the remainder to the volume determined as necessary by calculation from the assay, using a sufficient quantity of an alcohol and water mixture to provide the required proportion of C_2H_5OH. Mix thoroughly.

Process C—*Fractional or Divided Percolation.* This process is used for preparing fluidextracts, the constituents of which are injured by heat, or as an alternative for Process A or B, or in case suitable facilities for distillation and concentration are lacking. When Process C is used to prepare a fluidextract directed to be made by Process B, Menstruum I is used throughout the percolation.

Divide 1000 g. of the ground drug into three portions, consisting of 500 g., 300 g., and 200 g. Mix the first portion (500 g.) with sufficient of the prescribed menstruum to render it evenly and distinctly damp, transfer the dampened powder to a suitable percolator, the capacity of which should not greatly exceed the bulk of the moist drug when packed firmly, and allow it to stand for about 15 minutes. Then pack the drug in the percolator, saturate it with the menstruum, and allow it to macerate for the prescribed period of time. Then proceed with the percolation, first collecting and reserving 200 ml. of percolate, and afterwards collecting five successive 300-ml. portions of percolate, numbering them in the order in which they are obtained.

Dampen the second portion (300 g.) of the drug with a sufficient quantity of the first of the 300-ml. portions of percolate from the preceding lot of drug, and carry out the percolation as just directed for the first lot, except use the five 300-ml. portions of percolate from the first lot of drug as menstruum in the order in which they were received, followed, if necessary, by sufficient fresh menstruum to supply the following portions of percolate: reserve the first 300 ml. of percolate, and then collect five successive 200-ml. portions, numbering them in the order in which they are collected.

Now dampen the third portion (200 g.) of the drug with a sufficient quantity of the first numbered portion of percolate from the second lot of drug, and proceed with the percolation as before, using as the menstruum the 200-ml. portions of percolate from the second lot of drug in the order received. If no assay is directed, collect and reserve 500 ml. of percolate. Mix the three reserved percolates from the three lots of drug to make 1000 ml. of fluidextract.

If the fluidextract being prepared by Process C is to be adjusted to a standard, collect and reserve only 420 ml. of percolate from the third portion of drug instead of the 500 ml. directed above. Mix the three reserved percolates from the three lots of drug, and assay a portion of the mixture. Dilute the remainder to the volume determined as necessary by calculation from the assay, using a sufficient quantity of an alcohol and water mixture to provide the required proportion of C_2H_5OH. Mix thoroughly.

Process D—This process is used for preparing fluidextracts with boiling water as the menstruum, alcohol being added as a preservative to the concentrated percolate.

To 1000 g. of the coarsely ground drug add about 3000 ml. of boiling water, mix well, and allow it to macerate in a suitable, covered metallic percolator for 2 hours. Then allow the percolation to proceed at the specified rate, gradually adding boiling water until the drug is exhausted. Evaporate the percolate on a water bath, or in a vacuum still, to the volume specified, cool, add the alcohol, and allow the mixture to stand in a stoppered container for several days. Then decant the clear liquid, filter the remainder into the decanted liquid, and wash the residue on the filter with a sufficient quantity of a mixture of alcohol and water to make the fluidextract measure 1000 ml. and contain the required proportion of C_2H_5OH. Mix thoroughly.

Process E—This process is a modification of Process C, and can be used as an alternative for Processes A, B, or C. The percolation is conducted on a column of drug much greater in length than in diameter.

To 1000 g. of the ground drug add a sufficient quantity of the prescribed menstruum to render it evenly and distinctly damp. Allow the dampened drug to stand for about 15 minutes, then pack it into a cylindrical percolator or series of such percolators joined together and having a total length sufficient to insure practically complete extraction of the drug by the collection of 1000 ml. of percolate. Saturate the drug at a slow rate by forcing the menstruum through under pressure. Allow the drug to macerate for the prescribed period and proceed with percolation under pressure, at one-half the rate specified for the other type processes, adding fresh menstruum as needed. It is necessary to work out conditions of percolation for each drug. The alcohol content of the percolate from some drugs will exceed the limit specification in the monograph; therefore, in those cases it is desirable to reduce the alcohol content of the menstruum accordingly.

Packaging and Storage—Preserve Fluidextracts in tight, light-resistant containers and avoid exposure to direct sunlight or to excessive heat.

Gels

Gels are suspensions, in a water medium, of insoluble drugs in hydrated form wherein the particle size approaches or attains colloidal dimensions. A structural coherent matrix of the substances enclosing the water may be formed. Gels tend to separate on standing and may require a label directing that they be shaken well before each use. *Aluminum Hydroxide Gel* is an example of such a product. Milks (magmas) are almost identical with gels in their nature except that their particle size is somewhat larger. Jellies are a class of gels in which the structural coherent matrix contains a high proportion of liquid, usually water. *Ephedrine Sulfate Jelly* is an example of such a product.

Inhalants

Inhalants are drugs or combinations of drugs which, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The device making possible the administration of an inhalant is known as an *inhaler*. An example of such a product is *Propylhexedrine Inhalant*, which contains the volatile sympathomimetic, propylhexedrine.

Another group of products also known as inhalants or insufflations, consists of finely powdered or liquid drugs that are carried into the respiratory passages by the use of special devices. Such devices include the low-pressure "aerosol" containers, which hold a solution or suspension of the drug in a liquefied propellant such as a fluorine- or fluorine and chlorine-substituted hydrocarbon. When released through a suitable spray nozzle, a metered dose of the inhalant is propelled into the respiratory tract of the patient. (See also *Aerosols*.)

Inhalations

Inhalations are solutions for administration as a nebulized mist intended to reach the respiratory tree. *Isoproterenol Sulfate Inhalation* and *Epinephrine Inhalation* are examples of this dosage form. Nebulizers are suitable for the administration of inhalations only if they give a droplet size not exceeding a few microns. It is this form that produces the full therapeutic effect. See also *Aerosols*, page 825.

Injections—See *Injections*, page 810.

Liniments

Liniments are liquid preparations for external application or application to the gums. They may be clear dispersions, suspensions, or emulsions. Liniments of the suspension or emulsion type tend to separate or stratify on standing and require a label directing that they be shaken well before each use.

Lotions

Lotions are liquid suspensions or dispersions intended for external application to the body. Some, like *Calamine Lotion*, consist of finely powdered, insoluble solids held in more or less permanent suspension by the presence of suspending agents and/or surface-active agents. Others are emulsions of the oil-in-water type stabilized by a surface-active agent. Both types of lotions tend to separate or stratify on long standing, and require a label directing that they be shaken well before each use.

Milks

Milks (formerly called magmas) are suspensions of poorly soluble drugs in a water medium and are distinguished from gels mainly in that the suspended particles are larger. Thus they tend to separate on standing and require a label directing that they be shaken well before each use. An example of this type of dosage form is *Milk of Bismuth*.

Ointments

Ointments are semi-solid preparations usually containing medicinal substances and intended for external application to the body.

Ointment bases recognized for use as vehicles fall into four general classes: the hydrocarbon bases, the absorption bases, the water-removable bases, and the water-soluble bases. Each therapeutic ointment possesses as its base a representative of one of these four general classes.

Hydrocarbon Bases—These bases, which are known also as "oleaginous ointment bases," are represented by *Petrolatum* and *Yellow Ointment*. Only small amounts of an aqueous component can be incorporated into them. They serve to keep medicaments in prolonged contact with the skin and act as occlusive dressings. Hydrocarbon bases are used chiefly for their emollient effects, and are difficult to wash off. They do not "dry out" or change noticeably on aging.

Absorption Bases—This class of bases may be divided into two groups, the first group consisting of bases that permit the incorporation of aqueous solutions with the formation of a water-in-oil emulsion (*Hydrophilic Petrolatum* and *Anhydrous Lanolin*), and the second group consisting of water-in-oil emulsions that permit the incorporation of additional quantities of aqueous solutions (*Lanolin* and *Rose Water Ointment*). Some medicaments are absorbed somewhat better from these bases than from the hydrocarbon bases. Absorption bases are useful also as emollients.

Water-removable Bases—Such bases are oil-in-water emulsions, *e.g.*, *Hydrophilic Ointment*. They are described also as "water-washable," since they may be readily washed from the skin or clothing with water, an attribute that makes them more acceptable for cosmetic reasons. Medicaments such as local anti-infective agents and antibiotics may be more effective in these bases than in hydrocarbon bases. Other advantages of the water-removable bases are that they may be diluted with water and that they favor the absorption of serous discharges in dermatological conditions.

Water-soluble Bases—This group of so-called "greaseless ointment bases" is comprised of water-soluble constituents. *Polyethylene Glycol Ointment* is an example of such a product. Bases of this type offer many of the advantages of the water-removable bases and, in addition, contain no water-insoluble substances such as anhydrous lanolin, petrolatum, waxes, etc. Water, or a water solution, cannot be incorporated in this kind of base because of the resultant softening effect. The water-soluble bases may in some instances be irritating to inflamed tissue.

Choice of Base—The choice of an ointment base depends upon many factors, such as the nature of the medicament to be incorporated and its stability, the action desired, and the requisite shelf-life of the finished product. In some cases, it is necessary to use a base that is less than ideal pharmaceutically in order to achieve the stability required. Drugs that hydrolyze rapidly, for example, are more stable in hydrocarbon bases than in bases containing water, even though they may be more effective in the latter.

Ophthalmic Ointments—Ophthalmic ointments are special ointments for application to the eye. Special precautions must be taken in the preparation of an ophthalmic ointment. The medicinal agent is added to the ointment base either as a solution or as a micronized powder. The finished ointment must be free from large particles, and must meet the requirements for *Metal Particles—Ophthalmic Ointments*, page 816.

The ointment base that is selected must be nonirritating to the eye, permit diffusion of the drug throughout the secretions bathing the eye, and retain the activity of the medicament for a reasonable period under proper storage conditions.

Petrolatum is very frequently employed as a base for ophthalmic drugs. Some absorption bases, water-removable bases, and water-soluble bases may be desirable if a water-soluble medicament is used. Such bases allow for better dispersion of water-soluble medicaments, but they must not in themselves be irritating to the eye.

Ophthalmic Solutions

Ophthalmic solutions are sterile solutions, essentially free from foreign particles and suitably compounded and dispensed for instillation into the eye. Preparation of an ophthalmic solution requires careful consideration of such factors as the inherent toxicity of the drug itself, isotonicity value, the need for buffering agents, the need for a preservative (and, if needed, its selection), sterilization, and proper packaging.

Isotonicity Value—Lacrimal fluid is isotonic with blood, having an isotonicity value corresponding to that of a 0.9 percent sodium chloride solution. Ideally, an ophthalmic solution should have this isotonicity value; but the eye can tolerate isotonicity values as low as that of a 0.6 percent sodium chloride solution and as high as that of a 2.0 percent sodium chloride solution without marked discomfort.

Some ophthalmic solutions are necessarily hypertonic in order to provide a concentration strong enough to exert a prompt and effective action. Where the amount of such solutions used is small, dilution with lacrimal fluid takes place rapidly so that discomfort from the hypertonicity is only temporary. However, any adjustment toward isotonicity by dilution with tears is negligible where large volumes of hypertonic solutions are used as collyria to wash the eyes; it is therefore important that solutions used for this purpose be approximately isotonic.

Buffering—Many drugs, notably alkaloidal salts, are most effective at pH levels that favor the undissociated free bases. At such pH levels, however, the drug may be unstable so that compromise levels must be found and held by means of buffers. One purpose of buffering some ophthalmic solutions is to prevent an increase in pH caused by the slow release of hydroxyl ions by glass. Such a rise in pH can affect both the solubility and the stability of the drug. The decision whether or not buffering agents should be added in preparing an ophthalmic solution must be based on several considerations. Normal tears have a pH of about 7.4 and possess some buffer capacity. The application of a solution to the eye stimulates the flow of tears and the rapid neutralization of any excess hydrogen or hydroxyl ions within the buffer capacity of the tears. Many ophthalmic drugs, such as alkaloidal salts, are weakly acidic and have only weak buffer capacity. Where only 1 or 2 drops of a solution containing them are added to the eye, the buffering action of the tears is usually adequate to raise the pH and prevent marked discomfort. Some drugs, notably pilocarpine hydrochloride and epinephrine bitartrate, are more acid and overtax the buffer capacity of the lacrimal fluid. Ideally, an ophthalmic solution should have the same pH, as well as the same isotonicity value, as lacrimal fluid. This is not usually possible since, at pH 7.4, many drugs are not appreciably soluble in water. Most alkaloidal salts precipitate as the free alkaloid at this pH. Additionally, many drugs are chemically unstable at pH levels approaching 7.4. This instability is more marked at the high temperatures employed in heat sterilization. For this reason, the buffer system should be selected which is nearest to the physiologic pH of 7.4 and does not cause precipitation of the drug or its rapid deterioration.

An ophthalmic preparation with a buffer system approaching the physiologic pH can be obtained by mixing a sterile solution of the drug with a sterile buffer solution, using aseptic technique. Avoidance of heat sterilization limits immediate deterioration. Even so, the possibility of a shorter shelf-life at the higher pH must be taken into consideration, and attention must be directed toward the attainment and maintenance of sterility throughout the manipulations.

The following paragraphs present some vehicles commonly used in ophthalmologic practice. They are isotonic with tear fluid, but only the *Isotonic Phosphate Vehicle* possesses buffering capacity.

Boric Acid Vehicle—This vehicle has a pH slightly below 5.0. It may be prepared by dissolving 1.9 g. of boric acid in sufficient water to make 100 ml. of solution. This is suitable for the salts of the following substances:

Benoxinate
Cocaine
Dibucaine
Phenylephrine
Piperocaine
Procaine
Proparacaine
Tetracaine
Zinc

Special Boric Acid Vehicle—A modification of the *Boric Acid Vehicle* that is adapted to salts of physostigmine and epinephrine may be prepared by adding 100 mg. of sodium sulfite for each 100 ml. of solution. Consideration should be given to limited stability of sodium sulfite in this vehicle.

[Note—A suitable preservative, such as phenylmercuric nitrate or phenylmercuric acetate, in an appropriate concentration, should be used in both of the boric acid vehicles.]

Isotonic Phosphate Vehicle—The phosphate buffer system adjusted for isotonicity provides a choice of pH ranging from 5.9 to 8.0. This vehicle requires two stock solutions, one containing 8.00 g. of NaH_2PO_4 (monobasic sodium phosphate) per liter, and the other containing 9.47 g. of Na_2HPO_4 (dibasic sodium phosphate) per liter, the weights being on the anhydrous basis. The stock solutions are used in the proportions indicated in the following table:

Monobasic Sodium Phosphate Solution, ml.	Dibasic Sodium Phosphate Solution, ml.	Resulting Buffer Solution, pH	Sodium Chloride Required for Isotonicity, g./100 ml.
90	10	5.9	0.52
80	20	6.2	0.51
70	30	6.5	0.50
60	40	6.6	0.49
50	50	6.8	0.48
40	60	7.0	0.46
30	70	7.2	0.45
20	80	7.4	0.44
10	90	7.7	0.43
5	95	8.0	0.42

The vehicles listed in the foregoing table are satisfactory for many ophthalmic drugs, but since they are isotonic, the addition of drugs makes them hypertonic. If the amount of drug added is small, or if it exerts little osmotic effect, the resultant increase in tonicity is so slight as to cause minimal discomfort to the patient. Frequently, however, the increase is objectionable and it may be avoided by a two-step procedure: First, the weighed amount of sterile drug solid is dissolved in sterile, purified water to make a definite volume of an isotonic solution; and second, the resulting solution is made up to the final volume appropriate for the desired drug strength by the addition of the sterile, buffered isotonic vehicle containing an adequate concentration of a suitable preservative. Listed in the accompanying table are a number of drugs commonly used in ophthalmologic practice and the information required for the preparation of 100 ml. of a 1 percent isotonic buffered solution. The right column shows the volume of isotonic solution that 1.0 g. of the drug will yield when dissolved in water. Thus, starting with 1.0 g. of drug, sufficient sterile, purified water is added to give the indicated volume and the resulting solution is then made up to 100 ml. by the addition of sterile, buffered isotonic vehicle containing an adequate concentration of a suitable preservative. For solutions containing other than 1 percent of active ingredient, the requisite volume of solution can be calculated by direct proportion, with due regard for the solubility and other properties of the drug concerned.

Solutions of pilocarpine, eucatropine, scopolamine, and homatropine salts exhibit limited stability in *Isotonic Phosphate Vehicle*. Furthermore, attention should be directed toward the influence of drug concentration on the pH of the ophthalmic solution.

Sterilization—The sterility of solutions applied to an injured eye is of the greatest importance. Sterile preparations in special containers for individual use on one patient should be available in every hospital, office, or other installation where accidentally or surgically traumatized eyes are treated. While sterilization by autoclaving in the final container is preferable, the method of attaining sterility is determined primarily by the character of the particular product (see *Sterilization*, page 958).

Mention has been made of the fact that buffering certain drugs near the physiological pH range makes them quite unstable at high temperature. This must not be overlooked. The decision must be made whether to use a lower and less desirable pH from the physiologic standpoint, or to mix the previously sterilized drug solution and sterile buffer solution by aseptic technique. With the exception of basic salts of weak acids such as sodium fluorescein or sodium sulfacetamide, solutions of all of the common ophthalmic drugs in 1.9 percent boric acid can be autoclaved at 121° for 15 minutes without serious effect on their therapeutic activity.

Avoiding the use of heat by employing a bacteria-retaining filter is a valuable technique, provided caution is exercised in the selection, assembly, and use of the equipment. Single-filtration, disposable units are available and should be utilized wherever possible.

Preservation—Ophthalmic solutions may be packaged in multiple-dose containers when intended for the individual use of one patient and where the ocular

Drug (1.0 g.)	Volume of Isotonic Solution, ml.
Atropine Sulfate	14.3
Benoxinate Hydrochloride	20.0
Boric Acid	55.7
Butacaine Sulfate	22.3
Chloramphenicol Sodium Succinate	15.7
Chlorobutanol (hydrous)	26.7
Cocaine Hydrochloride	17.7
Dibucaine Hydrochloride	14.3
Ephedrine Hydrochloride	33.3
Ephedrine Sulfate	25.7
Epinephrine Bitartrate	20.0
Epinephrine Hydrochloride	32.3
Eucatropine Hydrochloride	20.0
Homatropine Hydrobromide	19.0
Homatropine Methylbromide	21.0
Neomycin Sulfate	12.3
Phenacaine Hydrochloride	22.3
Phenylephrine Hydrochloride	35.7
Phenylethyl Alcohol	27.7
Physostigmine Salicylate	17.7
Physostigmine Sulfate	14.3
Pilocarpine Hydrochloride	26.7
Pilocarpine Nitrate	25.7
Piperocaine Hydrochloride	23.3
Polymyxin B Sulfate	10.0
Potassium Penicillin G	20.0
Procaine Hydrochloride	23.3
Proparacaine Hydrochloride	17.6
Scopolamine Hydrobromide	13.3
Silver Nitrate	36.7
Sodium Bicarbonate	72.3
Sodium Biphosphate	44.3
Sodium Borate	46.7
Sodium Colistimethate	16.7
Sodium Fluorescein	34.3
Sodium Phosphate (dibasic, heptahydrate)	32.3
Sodium Sulfacetamide	25.7
Sodium Sulfadiazine	26.7
Sodium Sulfamerazine	25.7
Sodium Sulfathiazole	24.3
Streptomycin Sulfate	7.7
Tetracaine Hydrochloride	20.0
Tetracycline Hydrochloride	15.7
Zinc Sulfate	16.7

surfaces are intact. Even though sterile when dispensed, each solution must contain a suitable substance or mixture of substances to prevent the growth of, or to destroy, microorganisms accidentally introduced when the container is opened in use. Benzalkonium chloride, 0.01 percent (1 in 10,000), is frequently used for this purpose, but it is not invariably satisfactory because of incompatibility with anionic drugs or nonionic surfactants in high concentrations. Where nitrates or salicylates are used, benzalkonium chloride should be replaced with phenylmercuric nitrate or phenylmercuric acetate, 0.002 percent (1 in 50,000). Chlorobutanol and phenylethyl alcohol are alternative preservatives that may be used in concentrations of 0.5 percent. Chlorobutanol hydrolyzes to form hydrochloric acid, with a resultant decrease in the pH of its solutions. This decomposition occurs rapidly at high temperatures and slowly at room temperature, in unbuffered solutions that are neutral initially.

In concentrations tolerated by the tissues of the eye, all of the agents discussed in the foregoing are ineffective against some strains of *Pseudomonas aeruginosa*, an organism that can invade the abraded cornea and cause ulceration and blindness.

Where intended for use in surgical procedures, ophthalmic solutions, although they must be sterile, should not contain antibacterial agents, since they may be irritating to the ocular tissues.

Sodium fluorescein solution should be dispensed in a sterile, single-use container or in the form of a sterile, impregnated paper strip. The strip releases a sufficient amount of the drug for diagnostic purposes when touched to the eye being examined for a foreign body or a corneal abrasion. Contact of the paper with the eye may be avoided by leaching the drug from the strip onto the eye with the aid of sterile water or sterile sodium chloride solution.

Thickening agent—A suitable grade of methylcellulose (1 percent if the viscosity is 25 centipoises, or 0.25 percent if 4000 centipoises) or other suitable thickening agent occasionally is added to ophthalmic solutions to increase the viscosity and aid in holding the drug in contact with the tissue. Although difficulty may be encountered in sterilization or in filtration, the thickened ophthalmic solution must be free from visible particles.

Pastes

Pastes comprise two classes of ointment-like preparations intended for external application. One class is made from some hydrogel such as hydrated pectin. The other class, the fatty pastes, *e.g.*, *Zinc Oxide Paste with Salicylic Acid*, consists of thick, stiff ointments that do not ordinarily flow at body temperature, and therefore serve as protective coatings over the areas to which they are applied.

The fatty pastes are less greasy and more absorptive than ointments by reason of a high proportion of powdered medicaments having an affinity for water. These pastes tend to absorb serous secretions, and are less penetrating and less macerating than ointments, so they are preferred for acute lesions that have a tendency toward crusting, vesiculation, or oozing.

Pellets

Pellets are small, rod-shaped or ovoid-shaped, sterile dosage forms composed of essentially pure steroid hormones in compressed form, intended for subcutaneous implantation in body tissue. Pellets serve as a depot providing for the slow release of the hormone over an extended period of time. *Testosterone Pellets* represent an example of this dosage form. Pellets are packaged in individual, sterile vials.

Pills

When pill formulas official in this National Formulary are to be made with mechanical equipment into either pills or tablets, excipients other than those specified in the formula and harmless to the patient may be used, and the amounts of diluent may be varied to produce a mass best adapted for such equipment, provided the amounts of medicinal ingredients per pill are not changed.

A suitable coating for any specific purpose may be applied to any of the pills official in this National Formulary, provided the coating will disintegrate in the alimentary tract and is composed only of ingredients harmless to the patient.

Powders

Official powders are homogeneous dispersions of finely divided, relatively dry, particulate matter, consisting of one or more substances. The degree of fineness of powders, where this is specified, is related to passage of the material through standard sieves (see page 850), *e.g.*, *Furazolidone and Nifuroxime Powder*.

Solutions

Solutions are liquid preparations that contain one or several soluble chemical substances usually dissolved in water and that do not, by reason of their ingredients (*e.g.*, sucrose) or their method of preparation (*e.g.*, injections), fall into another group of National Formulary products. The solute is usually nonvolatile. Solutions are used for the specific therapeutic effect of the solute, either internally or externally. They vary widely as to composition, method of preparation, strength, potency, mode of administration, use, and dosage.

Solutions are prepared variously as follows: (1) by simple solution, *e.g.*, *Potassium Iodide Solution* and *Iodine Solution* (2) by chemical reaction, *e.g.*, *Magnesium Citrate Solution* and (3) by extraction.

Sterile isotonic solutions are available for use as irrigating fluids and in artificial organ baths. They differ from Injections in respect to packaging, since their containers may be designed to empty rapidly and may exceed the one-liter limit imposed upon containers for Injections.

See also *Ophthalmic Solutions*, page 832.

Spirits

Spirits are alcoholic or hydroalcoholic solutions of volatile substances. They are prepared usually by simple solution or by the admixture of the several ingredients. Some spirits serve as flavoring agents, *e.g.*, *Compound Orange Spirit*, while others have medicinal value, *e.g.*, *Aromatic Ammonia Spirit*. Reduction of the high alcoholic content of spirits by admixture with aqueous preparations often causes turbidity.

Spirits require storage in tight containers to prevent loss by evaporation.

Suppositories

Suppositories are solid bodies of various weights and shapes, adapted for introduction into orifices of the human body and usually melting, softening, or dissolving at body temperature. The vehicles usually employed are theobroma oil, glycerinated gelatin, or high molecular weight polyethylene glycols.

The suppository base employed has a marked influence on the effect produced by the active ingredient incorporated in it. Theobroma oil melts rapidly after it is inserted, whereas glycerinated gelatin dissolves slowly in the secretions of the body cavity into which it is inserted. Theobroma oil is not miscible with these secretions and fails to release certain drugs incorporated with it as readily as does glycerinated gelatin. As a result, the latter base is more suitable for a number of antiseptics. On the other hand, theobroma oil is superior for allaying irritation, as in preparations intended for treating hemorrhoids.

Glycerin Suppositories—See page 330 for formula.

Theobroma Oil Suppositories—Suppositories may be made with theobroma oil in the relatively solid state by incorporating the medicinal substance and working the homogeneous, plastic mass into the desired shape by hand on a tile or by compression using a suitable press.

The fusion method of preparing theobroma oil suppositories involves incorporating the medicinal substance in the oil, which has been melted by cautious heating. The desired shapes are formed by pouring the melt into appropriately prepared, suitable molds and allowing it to cool.

For suppositories containing chloral hydrate, phenol, or other substances that soften the vehicle, the melting point of the mixture may be raised by the addition of a suitable proportion of spermaceti or other suitable hardening agent. It is important that the finished suppositories melt at body temperature.

The approximate weights of suppositories prepared with theobroma oil are given below. Suppositories prepared from other bases vary in weight and generally are heavier than the weights indicated here.

Rectal Suppositories for adults are tapered and usually weigh about 2 g. each.

Vaginal Suppositories are usually globular or oviform in shape and weigh about 5 g. each.

Preserve suppositories with theobroma oil base in well-closed containers, preferably at a temperature below 30°.

Glycerinated Gelatin Suppositories—Medicinal substances may be incorporated into glycerinated gelatin suppositories by adding the prescribed quantities of them to a suppository mass compounded as follows:

> Weigh the medicinal substance into a tared container, add purified water to make a total of 10 g., and dissolve or mix, depending upon the solubility of the medicinal substance. Add 70 g. of glycerin, and mix. To the mixture add 20 g. of granular gelatin, mix carefully to avoid incorporating air, and heat on a steam bath until the gelatin is dissolved. Pour the melted mixture into molds, and allow to congeal.

Two types of gelatin are recognized in this National Formulary (see *Emulsions*, page 827), and the type most suitable for the drug to be incorporated in the suppository must be selected. Either Type A or Type B gelatin is satisfactory for many drugs, but in some instances one or the other type gives better results.

Type A gelatin is usually acid in reaction and cationic in character. Type B gelatin is less acid and, since its pH is usually somewhat above its isoelectric point, it is anionic in character. A recognition of these properties and resultant incompatibilities is essential both pharmaceutically and therapeutically for best results with suppositories using this base.

Preserve glycerinated gelatin suppositories in tight containers, preferably at a temperature below 35°.

Polyethylene Glycol Bases—Suitable mixtures of polyethylene glycols of various molecular weights yield suppositories that are entirely soluble in water and in the secretions of mucous membranes.

Suspensions (See also *Injections*, page 810)

Suspensions are preparations of finely divided drugs either intended for suspension in some suitable liquid vehicle prior to use or already in suspension in a liquid vehicle. As an example of the first type, *Oxytetracycline for Oral Suspension* may be cited. This is a finely subdivided oxytetracycline mixed with harmless suspending agents and flavors. It is intended to be diluted with the prescribed volume of water and mixed before it is dispensed by the pharmacist. It is then administered orally to the patient. The second, ready-to-use type is exemplified by *Sulfamethizole Oral Suspension*. In this, the sulfamethizole is already suspended in a liquid, flavored vehicle in a form suitable for oral administration.

Some suspensions are sterile and are intended for injection. These also may be of the two types already described, the one requiring mixture with a prescribed amount of water for injection before use by the designated parenteral route, and the other, a preparation already suspended in a suitable liquid vehicle and ready for parenteral use. *Sterile Chloramphenicol for Suspension* is an example of the first type; an example of the second type is *Sterile Progesterone Suspension*. Some sterile suspensions are intended for intramuscular use and others for subcutaneous injection, but suspensions are never given intravenously or intrathecally.

A third type of suspension is that intended for ophthalmic use. This is a sterile suspension in an aqueous medium containing a suitable bacteriostatic agent.

By its very nature, the particulate matter of a suspension tends to settle slowly from the liquid vehicle in which it is dispersed, since its density is almost always greater than that of the liquid vehicle. In some cases, an added inert suspending agent is permitted to retard such sedimentation. In one, *Sterile Procaine Penicillin G with Aluminum Stearate Suspension*, a thixotropic gel exists which retards sedimentation.

It is important that suspensions be shaken well before each use to ensure a uniform distribution of solid in the vehicle and, thereby, uniform and proper dosage.

Syrups

Syrups are concentrated solutions of a sugar such as sucrose in water or other aqueous liquid. When purified water alone is used in making a nearly saturated solution of sucrose, the product is known as syrup or "simple syrup." In addition to sucrose, certain other polyols, such as glycerin or sorbitol, are sometimes present to retard crystallization of sucrose and for other reasons. When the aqueous liquid contains some added medicinal substance, the product is described as a medicated syrup, *e.g., Dextromethorphan Hydrobromide Syrup*.

Some so-called syrups contain sweetening agents other than sucrose or other sugars, and they contain thickening agents, such as cellulose derivatives. *Acacia Syrup* is an example of a syrup in which part of the sucrose has been replaced by a thickening agent. Viscid, sweetened solutions containing no sugars occasionally are prepared as vehicles for drugs administered to diabetic patients.

Tablets

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. Different tablets vary in shape and differ greatly in size and weight, depending on the amount of the medicinal substance and the intended mode of administration.

Tablets may be classed, according to the method of manufacture, as molded tablets or compressed tablets.

The preparation of compressed tablets is almost exclusively a large-scale production process. Whereas molded tablets are generally made with manual pressure, compressed tablets are made using great pressure, thus requiring heavy machinery.

Tablet triturates are small, usually cylindrical, molded or compressed disks of various sizes. They are prepared from the medicinal substance and a diluent usually consisting of dextrose or of a mixture of lactose and powdered sucrose in varying proportions. A moistening agent, such as a diluted alcohol, is used also. The greater the solubility of the medicinal substance in water, the greater must be the percentage of alcohol in the excipient, but with drugs of low solubility in water, equal amounts of water and alcohol may be used. The tablets are formed by forcing the dampened tablet material into a mold, with subsequent ejection and drying.

Compressed tablets or molded tablets known as "hypodermic tablets," which dissolve completely in water, are available for the preparation of injectable solutions. The difficulties of preparing sterile, suitably clear solutions from such tablets offset in large measure the convenience claimed for the tablets.

Buccal and sublingual tablets are small, flat, oval dosage forms intended to be inserted either in the buccal pouch or beneath the tongue, where the active ingredient is absorbed directly without being required to pass into the gastrointestinal tract. Few drugs are readily absorbed in this way, but for those which are (such as erythrityl tetranitrate and certain steroid hormones), a number of advantages may result. Tablets intended for buccal administration dissolve or disintegrate slowly, while those for sublingual use dissolve very promptly.

Dispensing tablets are prepared either by molding or by compression. They contain relatively large amounts of drug and are not intended for use as a dosage form, but are supplied as a convenience to the dispensing pharmacist for obtaining quantities of certain potent substances in a suitable form for accurate compounding.

Soluble, effervescent tablets are a popular form of dispensing the noncaloric sweetening agents. The effervescence speeds the process of solution.

Most compressed tablets consist of the active ingredient and a diluent, binder, disintegrator, and lubricant. Different tablets vary greatly in size, and diluents are added when the quantity of active ingredient is small. Binders give adhesiveness to the powder during the preliminary granulation. A disintegrator, such as starch, serves to ensure the fragmentation of the tablet and thus promote rapid release of the medication. Lubricants prevent the material from adhering to the dies and punches during compression.

Certain diluents or excipients, such as mannitol, lactose, or inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets are commonly called "chewable tablets." Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel, and leave no unpleasant aftertaste in the mouth.

Coatings, if used, usually consist mainly of sugar or other suitable, soluble substances, but clear, plastic coatings are used also. For purposes of identification or patient acceptance, the coatings may be colored. The finished coated tablets are sometimes polished, usually by applying a wax.

Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach.

Less well-defined are tablets variously known as "delayed-action," "prolonged-action," "sustained-action" or "repeat-action" preparations, the object of which is to make the contained medicament available over an extended period of time after ingestion. Official recognition of tablets of this class includes only those specifically identified as "enteric-coated."

Sure disintegration is an essential attribute of all tablets intended for administration by mouth. For this reason, a disintegration test is provided (see page 878), and limits on the time in which disintegration is to take place, appropriate for the types of tablets concerned, are given in the individual monographs.

Tinctures

Tinctures are alcoholic or hydroalcoholic solutions prepared from animal or vegetable drugs or from chemical substances.

The proportion of drug represented in the different tinctures is not uniform but varies according to the established standards for each. Tinctures of potent drugs essentially represent the activity of 10 g. of the drug in each 100 ml. of tincture. Most of the other tinctures represent 20 g. of the respective drugs in each 100 ml. of tincture. Compound tinctures are made according to long established formulas.

The general processes to be employed for the manufacture of tinctures, unless otherwise directed in the individual monographs, are as follows:

Process P—Carefully mix the ground drug or mixture of drugs with a sufficient quantity of the prescribed menstruum to render it evenly and distinctly damp, allow it to stand for 15 minutes, transfer it to a suitable percolator, and pack the drug firmly. Pour on enough of the prescribed menstruum to saturate the drug, cover the top of the percolator, and when the liquid is about to drip from the percolator, close the lower orifice, and allow the drug to macerate for 24 hours or for the time specified in the monograph. If no assay is directed, allow the percolation to proceed slowly, or at the specified rate, gradually adding sufficient menstruum to produce 1000 ml. of tincture, and mix thoroughly.

If an assay is directed, collect only 950 ml. of percolate; mix this thoroughly, and assay a portion of it as directed. Dilute the remainder with such a quantity of the prescribed menstruum as calculation from the assay indicates is necessary to produce a tincture that conforms to the prescribed standard. Mix well. The rate of flow of percolates is defined under *Fluidextracts*, page 829.

Process M—Macerate the drug or mixture of drugs in a container which can be closed, in a moderately warm place, with 750 ml. of the prescribed menstruum, agitating it frequently for 3 days or until the soluble matter is dissolved. Transfer the mixture to a filter, and when most of the liquid has drained away, wash the residue on the filter with a sufficient quantity of the prescribed menstruum, combining the filtrates, to produce 1000 ml. of tincture. Mix the product well.

Packaging and Storage—Preserve Tinctures in tight, light-resistant containers and avoid exposure to direct sunlight and to excessive heat.

Waters—See *Aromatic Waters*

PHASE SOLUBILITY ANALYSIS

Phase solubility analysis is the quantitative determination of the purity of a substance through the application of precise solubility measurements. At a given temperature, a definite amount of a pure substance is soluble in a definite quantity of solvent. The resulting solution is saturated with respect to the particular substance but the solution remains unsaturated with respect to other substances even though such substances may be closely related in chemical structure and physical properties to the particular substance being tested. Constancy of solubility, just as constancy of melting point or other physical properties, indicates that a material is pure or free from foreign admixture except in the unique case where the percentage composition of the sample being tested is in direct ratio to solubilities of the respective components. Conversely, variability of solubility indicates the presence of an impurity or impurities.

Phase solubility analysis is applicable to all species of compounds which form stable solutions.

The standard solubility method consists of six distinct steps: (1) mixing, in a series of separate systems, increasing quantities of material with measured, fixed amounts of a solvent; (2) establishment of equilibrium for each system at identical constant temperature and pressure; (3) separation of the solid phase from the solutions; (4) determination of the concentration of the material dissolved in the various solutions; (5) plotting the concentration of the dissolved materials per unit of solvent (y axis or solution composition) against the weight of material per unit of solvent (x axis or system composition); and (6) extrapolation and calculation.

Solvents

The following criteria are used in the selection of a proper solvent for phase solubility analysis: (1) The solvent should be of sufficient volatility so that it can be evaporated under vacuum, but it should not be so volatile that difficulty is experienced in transferring and weighing the solvent and its solutions. Normally, solvents with boiling points between 60° and 150° are suitable. (2) The solvent should not adversely affect the sample. Solvents which cause decomposition or react with the sample cannot be used. Solvents which solvate or form salts should be avoided if possible. (3) The solvent should be of known purity and composition. Carefully prepared mixed solvents are permissible. Trace impurities may affect solubility greatly. (4) The sample should be soluble to the extent of not less than 4 mg. per ml. and not more than 50 mg. per ml. in the solvent chosen. A solubility of 10 to 20 mg. per ml. is optimal.

Apparatus

Constant-temperature Bath—For these tests use a constant-temperature bath capable of maintaining a temperature of 25 ± 0.1°, equipped with a horizontal shaft capable of rotating at approximately 25 r.p.m. The shaft is equipped with clamps to hold the *Ampuls.*

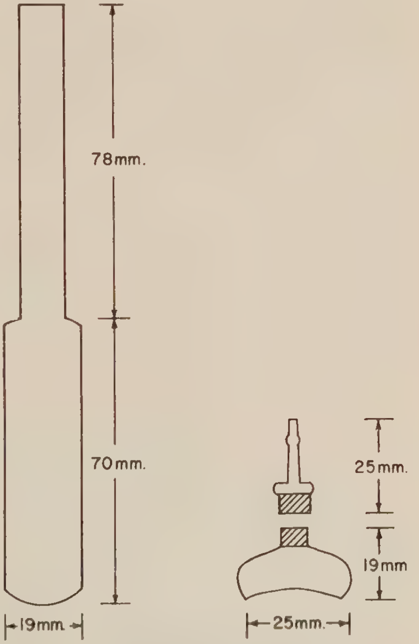
Ampuls—Use 15-ml. ampuls similar to that shown in the accompanying illustration. Other containers may be used provided that they are leakproof and are suitable in all other respects.

Solubility Flasks—Use solubility flasks similar to that shown in the accompanying illustration.

Procedure

(Note: Make all weighings within ± 10 mcg.)

System Composition—Weigh accurately, in g., not less than 7 scrupulously cleaned, 15-ml. ampuls. Weigh accurately, in g., increasingly larger amounts of the test substance into each of the ampuls. The weight of the test substance is selected so that the first ampul contains slightly less material than will go into solution in 5 ml. of the selected solvent, and the second ampul and subsequent ampuls slightly



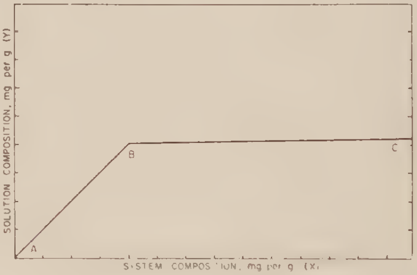
Ampul (left) and Solubility Flask (right) Used in Phase Solubility Analysis more than the indicated solubility. Pipet 5.0 ml. of the solvent into each of the ampuls, cool in a dry ice-acetone mixture, and seal, using a double jet air-gas burner taking care to save all glass. Allow the ampuls plus their contents to come to room temperature, and weigh the individual sealed ampuls with the corresponding glass fragments. Calculate the system composition, in mg. per g., for each ampul by the formula $1000(W_2 - W_1)/(W_3 - W_2)$, in which W_1 is the weight of the empty ampul, W_2 is the weight of the ampul plus test substance, and W_3 is the weight of ampul plus test substance, solvent, and separated glass.

Equilibration—Unless otherwise specified in the individual monograph, effect equilibration by rotating the ampuls end-over-end in the constant-temperature bath. The time required for equilibration in the rotating procedure varies from 7 to 14 days, depending upon the nature of the substance being tested. In order to determine if equilibration has been effected, one ampul—the next to the last in the series—may be warmed to 40° to produce a supersaturated solution. Equilibration is assured if the solubility obtained on the supersaturated solution falls in line with the samples which approach equilibrium from an undersaturated solution. A vibration procedure is useful, in special cases, in effecting more rapid equilibration.

Solution Composition—After equilibration, place the ampuls vertically in a rack in the constant-temperature bath, with the necks of the ampuls above the water level, and allow the contents to settle. Open the ampuls, and remove a 2.0-ml. portion from each by means of a pipet equipped with a small pledget of cotton to serve as a filter. Remove the cotton, transfer the aliquot of clear solution from each ampul to a marked, tared solubility flask, and weigh each flask plus its solution to obtain the weight of the solution. Cool the flasks in a dry ice-acetone bath, and then evaporate the solvent in a vacuum. Gradually increase the temperature to 70° to 100°, and dry the residue to constant weight. Calculate the solution composition, in mg. per g., by the formula $1000(F_3 - F_1)/(F_2 - F_3)$, in which F_1 is the weight of the solubility flask, F_2 is the weight of the flask plus solution, and F_3 is the weight of the flask plus residue.

Calculation

For each portion of the test substance taken, plot the solution composition as the ordinate and the system composition as the abscissa. As shown in the accompanying diagram, the points for those containers which represent a true solution should fall on a straight line (AB) with a slope of 1, passing through the origin; the points corresponding to saturated solutions should fall on another straight line (BC), the slope, S, of which represents the fraction of impurity or impurities present in the test substance. Failure of points to fall on a straight line indicates that equilibrium has not been achieved. Calculate the percent purity of the test substance by the formula $100 - 100S$. The slope may be calculated by the formula $(Y_2 - Y_1)/(X_2 - X_1)$, in which Y_2 and Y_1 represent solution compositions, and X_2 and X_1 represent the respective system compositions, at convenient points on the second straight line.



Typical Phase Solubility Diagram

The solubility of the main component is obtained by extending the solubility line (BC) through the Y-axis. The point of interception on the Y-axis is the extrapolated solubility, in mg. per g., and should be constant for a given compound.

PLASTICS—CONTAINERS FOR INJECTIONS

Plastics can be of synthetic or natural origin and are generally divided into two broad categories in accordance with their response to applied heat; they may be satisfactorily described as being either thermoplastic or thermosetting. A *thermoplastic* material is usually rigid at normal temperatures but will soften upon the application of heat and deform under pressure. A *thermosetting* material, on the other hand, will undergo chemical and physical changes under the influence of heat or catalysts to become substantially infusible and insoluble. Few plastics are single chemical entities. In general, a commercial plastic consists of a mixture of homologous compounds having a range of molecular weights. Such plastics

Table I. Classification of Plastics

Plastic Classes*						Tests to be Conducted				
I	II	III	IV	V	VI	Sample to be used	Animal	Dose	Route†	Procedure‡
X	X	X	X	X	X	Extract of plastic in sodium chloride injection	Mouse	50 ml./kg.	I.V.	A
X	X	X	X	X	X		Rabbit	10–0.2 ml./animal	I.C.	B
	X	X	X	X	X	Extract of plastic in alcohol (5%) and sodium chloride (0.9%) in water for injection	Mouse	50 ml./kg.	I.V.	A
	X	X	X	X	X		Rabbit	10–0.2 ml./animal	I.C.	B
		X		X	X	Extract of plastic in polyethylene glycol 400	Mouse	10 g./kg.	I.P.	A
				X	X		Rabbit	10–0.2 ml./animal (24 mg./0.2 ml.)	I.C.	B
		X	X	X	X	Extract of plastic in sesame oil¶	Mouse	50 ml./kg.	I.P.	A
			X	X	X		Rabbit	10–0.2 ml./animal	I.C.	B
			X		X	Implant strips of the plastic specimen	Rabbit	Four 1 mm. × 10 mm. strips/animal	I.M.	C

* Tests required for each class indicated by X in appropriate columns.

† Route: I.C.—Intracutaneous; I.M.—Intramuscular; I.P.—Intraperitoneal; I.V.—Intravenous.

‡ Test Procedure: A—Acute Systemic Toxicity; B—Intracutaneous Reactivity; C—Acute Intramuscular Tissue Toxicity.

¶ Cottonseed oil may be used instead of sesame oil.

frequently contain other substances such as residues from the polymerization process, plasticizers, stabilizers, antioxidants, pigments, and lubricants.

Definitions

For the purpose of this chapter these definitions apply: A *container* is the device which holds the drug and which is or may be in direct contact with the drug. The *sample* is the plastic specimen under test or the extract prepared from such a specimen. A *blank* consists of the same quantities of the same extracting medium used for the extraction of the specimen under test treated in the same manner as the extracting medium containing the specimen under test. A *negative control*§ is a plastic specimen which gives no reaction under the conditions of the test.

Classification of Plastics

On the basis of response to the biological test procedures (see page 841), six general classes of plastics are defined in Table I. This classification does not apply to plastics which are intended for use as containers for oral or topical products, or which may be used as an integral part of a drug formulation.

Factors such as plastic composition, processing, cleaning procedures, contacting media, inks, adhesives, and conditions of storage may also affect the suitability of a plastic for a specific use. Evaluation of such factors should be made by appropriate additional specific tests to determine the suitability of a plastic for its intended use.

With the exception of the implantation test, the procedures are based on the use of extracts which, depending on the heat resistance of the plastic, are prepared at one of three standard temperatures: 50°, 70°, or 121°. Therefore, the class designation of a plastic must also indicate the temperature of extraction, *e.g.*, IV-121°, which would represent a class IV plastic extracted at 121°, or I-50°, which would represent a class I plastic extracted at 50°.

Biological Test Procedures

The following tests are designed to determine the biological response of animals to plastics by the single-dose injection of specific extracts prepared from a plastic or by the implantation of the plastic itself into animal tissue. It is essential not only to use the designated amount of the plastic, but also to make available the specified surface for extraction at the particular temperature. Also, it is essential to exercise care in the preparation of the materials to be injected to prevent contamination with microorganisms and other foreign matter.

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§ Specimens of Negative Control Plastic for use as negative controls are available on order from USP Reference Standards, 4630 Montgomery Avenue, Bethesda, MD 20014.

The tests are designed for plastics in the condition in which they are received. If, however, a plastic is to be exposed to any sterilization process prior to its end use, then the tests are conducted on plastics preconditioned by the appropriate sterilization procedure.

Extracting Media—Sodium chloride injection; alcohol (5%) and sodium chloride (0.9%) in water for injection; sesame oil (Note: cottonseed oil may be used instead of sesame oil); polyethylene glycol 400.

Apparatus

Autoclave—For these tests use an autoclave capable of maintaining a temperature of 121 ± 0.5°, equipped with a thermometer, a pressure gauge, a vent cock, a rack adequate to accommodate the test containers above the water level, and a water cooling system which will allow for cooling of the test containers to about, but not below, 22° immediately following the heating cycle.

Oven—Use an oven, preferably a forced-draft model, which will maintain operating temperatures of 70° or 50° within ±1°.

Extraction Containers—Use only containers, such as ampuls or screw cap culture test tubes, of Type I glass. If used, culture test tubes are closed with a screw cap having a suitable rubber liner. The exposed surface of the rubber liner is completely protected with an inert solid disk 0.05 mm. to 0.075 mm. in thickness. A suitable disk can be fabricated from a polytetrafluoroethylene resin.

Preparation of Apparatus—Clean all glassware thoroughly with chromic acid cleansing mixture and, if necessary, with hot nitric acid followed by prolonged rinsing with distilled water. Clean cutting devices by an appropriate method (*e.g.*, successive cleaning with acetone and methylene chloride prior to subdividing a specimen). Clean all other equipment by thorough detergent scrubbing and prolonged rinsing with distilled water.

Render containers and devices used for extraction and in transfer and administration of test material sterile and dry by a suitable process. If ethylene oxide is used as the sterilizing agent, then allow adequate time for complete degassing.

Procedure

Preparation of Sample—From a homogeneous plastic sample use a portion equivalent to 120 cm.^{2} when the thickness is 0.5 mm. or less, or 60 cm.^{2} when the thickness is greater than 0.5 mm.; subdivide into strips approximately 0.3 cm. wide and as near to 5 cm. in length as is practical. Remove particulate matter, such as lint and free particles, by treating each subdivided sample as follows: Place the cuts in a clean 100-ml., glass-stoppered, graduated cylinder of Type I glass, and add about 70 ml. of water for injection. Agitate for about 30 seconds and drain off the water, repeat this step, and dry those pieces prepared for the extraction with sesame oil in an oven at a temperature not exceeding 50°. [Note: Do not clean the plastic with a dry or wet cloth or by rinsing or washing with an organic solvent, surfactant, etc.]

Extracts—Place two properly prepared *samples* of the plastic to be tested in separate extraction flasks, and add to each flask 20 ml. of the appropriate extracting medium. Repeat these directions for each extracting medium required for testing. Also prepare one 20-ml. blank of each medium for parallel injections and comparisons. Extract by heating in an autoclave at 121° for 60 minutes, in an oven at 70° for 24 hours, or at 50° for 72 hours. Allow adequate time for the liquid within the container to reach the extraction temperature.

[Note: The extraction conditions should not in any instance cause physical changes such as fusion or melting of the plastic pieces, which result in a decrease in the available surface area. A slight adherence of the pieces can be tolerated. Always add the cleaned pieces individually to the extracting medium. If culture tubes are used for autoclave extractions with sesame oil, seal screw caps adequately with pressure sensitive tape.]

Cool all containers at the end of the extraction period to about, but not below 22°. Agitate vigorously for several minutes, and then transfer each extract immediately to a dry, sterile container, and test within the following 24 hours. [Note: No extract should be stored at any time at temperatures below 22°.]

Implant Strips—Prepare for implantation 8 strips of the sample and 4 strips of the negative control.

Acute Systemic Toxicity and Intracutaneous Reactivity Tests

The acute systemic toxicity test and the intracutaneous reactivity tests are designed for the evaluation of extracts of a plastic material in mice or rabbits. Of importance is the contact of the extracting medium with the available surface area of the plastic and the time and temperature during extraction, the proper cooling, agitation and decanting process, as well as the aseptic handling and storage of the extracts following extraction.

[Note: Each extract must be agitated vigorously prior to withdrawal of each injection dose to ensure even distribution of the extracted matter.]

Acute Systemic Toxicity Test

Test Animal—Use healthy, not previously used albino mice weighing between 17 and 23 g. For each test group use only mice of the same source. Offer water and food, commonly used for laboratory animals and known as to composition, *ad libitum*.

Procedure—Inject into groups of 5 mice each the extract of the *sample* and the *blank* as outlined in Table II.

Table II. Injection Procedure

Extract or Blank	Dose per kg.	Route	Injection Rate (ml./sec.)
Sodium chloride injection	50 ml.	I.V.	0.1
Alcohol (5%) and sodium chloride (0.9%) in water	50 ml.	I.V.	0.1
Polyethylene glycol 400	10 g.	I.P.	. . .
Sesame oil	50 ml.	I.P.	. . .

Observe the animals immediately after injection, and at least at 24, 48, and 72 hours. If during the observation period all 5 of the animals treated with the extract of the *sample* show no significantly greater reaction than the animals treated with the *blank*, the *sample* meets the requirements of this test.

If any animals treated with the *sample* show only slight signs of toxicity, and not more than one animal shows gross symptoms of toxicity or death, repeat the test using groups of 10 mice. On the repeat test, all 10 animals treated with the *sample* should show no significant reaction above the *blank* animals during the observation period.

Intracutaneous Reactivity Test—[Note: The sesame oil meets the following additional requirements: Obtain, if possible, freshly refined oil. Use 3 properly prepared animals and inject the oil intracutaneously in a dose of 0.2 ml. into each of 10 sites per animal and observe the animals at 24, 48, and 72 hours following injection. No site should show a tissue reaction, such as edema and erythema, which is larger than 0.5 cm. in over-all diameter.]

Test Animal—Select healthy, thin-skinned albino rabbits not previously used for any test, whose fur can be clipped closely and whose skin is free from mechanical irritation or trauma. In handling the animals, avoid touching the injection sites during observation periods.

Procedure—On the day of the test, closely clip or re-clip the fur on the animal's back on both sides of the spinal column over a sufficiently large test area. Avoid mechanical irritation and trauma. Remove loose hair by means of vacuum. If necessary, swab the skin slightly with diluted alcohol and dry the skin prior to injection.

For each *sample* use two animals and inject each intracutaneously, using one side of the animal for the *sample* and the other side for the *blank*, as outlined in Table III.

Table III. Intracutaneous Injection Procedure

Extract or Blank	Number of Sites (per animal)	Dose* (ml./site)
Sample	10	0.2
Blank	5	0.2

* Dilute extracts and blanks prepared with polyethylene glycol 400 with sodium chloride injection to 24 mg. per 0.2 ml.

Examine injection sites for evidence of any tissue reaction such as erythema, edema, and necrosis. Swab the skin slightly, if necessary, with diluted alcohol to facilitate reading of injection sites. Observe all animals at 24, 48, and 72 hours after injection. Re-clip the fur as necessary during the observation period.

If each animal at any observation period shows an average reaction to the *sample* which is not significantly greater than to the *blank*, the *sample* meets the requirements of this test.

If at any observation period the average reaction to the *sample* is questionably greater than the average reaction to the *blank*, repeat the test using 3 additional rabbits. On the repeat test, the average reaction to the *sample* in any of the 3 animals should not be significantly greater than to the *blank*.

Acute Intramuscular Tissue Toxicity Test

The acute intramuscular tissue toxicity test is designed for the evaluation of a plastic material in direct contact with living tissue. Of importance is the proper preparation of the implant strips and their proper implantation under aseptic conditions. Prepare for implantation 8 strips of the sample and 4 strips of the *negative control*. Each strip should be not less than 10 × 1 mm. The edges of the strips should be as smooth as possible to avoid additional mechanical trauma upon implantation. Strips of the specified minimum size are implanted by means of a hypodermic needle such as a 15-gauge needle with I.V. point and of 19 mm. (0.75 in.) cannula length, and a sterile trocar. Use either presterilized needles into which the sterile plastic strips are aseptically inserted, or insert each clean strip into a needle, the cannula and hub of which is protected with an appropriate cover, and then subjected to the appropriate sterilization procedure. [Note: Allow for proper degassing if agents such as ethylene oxide are used.]

Test Animal—Select healthy, adult rabbits weighing not less than 2.5 kg., and whose paravertebral muscles are sufficiently large in size to allow for implantation of the test strips. Do not use any muscular tissue other than the paravertebral site. The animals may be anesthetized with a commonly used anesthetic agent to a degree deep enough to prevent muscular movements, such as twitching.

Procedure—Perform the test in a clean area. On the day of the test or up to 20 hours before testing, clip the fur of the animals on both sides of the spinal column. Remove loose hair by means of vacuum.

Implant 4 strips of the *sample* into the paravertebral muscle on one side of the spine of each of 2 rabbits, 2.5 to 5 cm. from the midline and parallel to the spinal column, and about 2.5 cm. apart from each other. In a similar fashion implant 2 strips of the *negative control* in the opposite muscle of each animal. Insert a sterile stylet into the needle to hold the plastic strip in the tissue while withdrawing the needle. If excessive bleeding is observed after implantation of a strip, place a duplicate at another site.

Keep the animals for a period of not less than 72 hours. Sacrifice the animals at the end of the observation period by administering an overdose of an anesthetic agent. Avoid bleeding of the animals by performing an autopsy after a sufficient time has lapsed. Examine macroscopically the area of the tissue surrounding the center portion of each implant strip. Use a magnifying glass if necessary.

The tissue immediately surrounding the negative control strips should appear normal and entirely free of hemorrhage, film, or encapsulation. The *sample* meets the requirements of this test if the reaction at 3 of the 4 sites in each animal is not significantly greater than that at the *negative control* sites.

Chemical Test Procedures

The following tests are designed to determine the chemical properties of plastics of the specific extracts prepared from the plastic. It is essential not only to use the designated amount of the plastic, but also to make available the specified surface area for extraction.

Extracting Medium—Water for injection.

Apparatus

Oven—Use an oven, preferably a forced-draft model, which will maintain an operating temperature of 70° ± 1°.

Extraction Containers—Use *Extraction Containers* as described on page 842.

Preparation of Apparatus—Prepare the apparatus as described in the first paragraph under *Preparation of Apparatus*, page 842, except the containers and devices need not be sterile.

Procedure

Preparation of Sample—From a homogeneous plastic sample, use a portion, for each 20.0 ml. of extracting medium, equivalent to 120 cm.^{2} when the thickness is 0.5 mm. or less, or 60 cm.^{2} when the thickness is greater than 0.5 mm.; subdivide into strips approximately 0.3 cm. wide and as near to 5 cm. in length as is practical. Transfer the subdivided sample to a 250-ml. glass-stoppered, graduated cylinder of Type I glass, and add about 150 ml. of water for injection. Agitate for about 30 seconds, drain off the water for injection, and repeat with a second washing.

Extracts—Transfer the prepared sample into a suitable extraction flask, and add the required amount of water for injection. Extract by heating in an oven at 70° for 24 hours. Allow adequate time for the liquid within the container to reach the extraction temperature. Cool, but not below 22°. Decant the extract immediately into a suitably cleansed container, and seal.

Blank—Use water for injection where a blank is specified in the following tests.

Nonvolatile Residue—Tare a suitable crucible, such as fused silica crucibles properly cleaned with acid, that has been dried to constant weight under the same conditions to be employed in the determination. Transfer 50.0 ml. of the *sample* extract in portions to the crucible, and evaporate the volatile matter on a steam bath. Dry the crucible at 105° to constant weight, cool, and weigh. (Note: If an oily residue is obtained, inspect the crucible repeatedly during the evaporation and drying period since such oils may creep along the walls of the crucible.) Perform a blank determination. The difference between the amounts obtained for the *sample* and the *blank* does not exceed 15.0 mg.

Residue on Ignition—Unless otherwise directed, add to the *sample* and the *blank* residues obtained under *Nonvolatile Residue* 0.5 ml. of sulfuric acid. Ignite, gently at first, until the substance is thoroughly charred or the carbon is completely consumed. If necessary, use additional sulfuric acid. When the carbon has completely disappeared, continue the ignition to constant weight, cool the crucibles in a desiccator, and weigh. The difference between the amounts obtained from the *sample* and the *blank* does not exceed 5.0 mg.

Heavy Metals—Unless otherwise directed, test for heavy metals as follows.

Solution A—Pipet into a 50-ml. Nessler tube, 20.0 ml. of the *sample* extract. Add 2 ml. of diluted acetic acid, and sufficient water to make 25 ml. If the extract is turbid, clarify by centrifugation or filtration.

Solution B—Pipet into a 50-ml. color comparison tube that matches the one used for *Solution A*, 2.0 ml. of diluted acetic acid, 20.0 ml. of the *blank*, and 2.0 ml. of *Standard Lead Solution*, and add water to make 25 ml. Add 10 ml. of hydrogen sulfide T.S. to each tube, mix, allow to stand for 10 minutes, and view downward over a white surface: the color of *Solution A* is no darker than that of *Solution B* (1 part per million).

Reaction—Unless otherwise directed, transfer 20.0 ml. of the sample extract, prior to decanting the extracted liquid sample from the extraction container, to a suitable container, and titrate potentiometrically to pH 7.0 with either 0.01 *N* sodium hydroxide or with 0.01 *N* hydrochloric acid as may be required. Treat 20 ml. of the *blank* similarly. The difference between the *sample* and the *blank* is not more than 0.10 milliequivalent per 20.0 ml. of extract.

PLASTICS—CONTAINERS FOR OPHTHALMICS

Plastics for ophthalmics are composed of a mixture of homologous compounds having a range of molecular weights. Such plastics frequently contain other substances such as residues from the polymerization process, plasticizers, stabilizers, antioxidants, pigments, and lubricants. Factors such as plastic composition, processing and cleaning operations, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. Evaluation of such factors should be made by appropriate additional specific tests to determine the suitability of a plastic for use as a container for ophthalmics.

Definitions

For the purpose of this chapter these definitions apply: A *container* is the device which holds the drug and which is or may be in direct contact with the drug. The *sample* is the plastic specimen under test or the extract prepared from such a specimen. A *blank* consists of the same quantities of the same extracting medium used for the extraction of the specimen under test treated in the same manner as the extracting medium containing the specimen under test.

Biological Test Procedures

The following tests are designed to determine the biological response of animals to plastics by the single-dose injection of specific extracts prepared from a plastic or by the instillation of the extract into the eye. It is essential not only to use the designated amount of the plastic, but also to make available the specified surface for extraction at the particular temperature. Also, it is essential to exercise care in the preparation of the materials to be injected to prevent contamination with microorganisms and other foreign matter.

The tests are designed for plastics in the condition in which they are received. If, however, a plastic is to be exposed to any sterilization process prior to its end use then the tests are conducted on plastics preconditioned by the appropriate sterilization procedure.

Apparatus

Autoclave—For these tests use an autoclave capable of maintaining a temperature of 121 ± 0.5°, equipped with a thermometer, a pressure gauge, a vent cock, a rack adequate to accommodate the test containers above the water level, and a water cooling system which will allow for cooling of the test containers to about, but not below, 22° immediately following the heating cycle.

Oven—Use an oven, preferably a forced-draft model, which will maintain operating temperatures of 70° or 50° within ±1°.

Extraction Containers—Use only containers, such as ampuls or screw cap culture test tubes, of Type I glass. If used, culture test tubes are closed with a screw cap having a suitable rubber liner. The exposed surface of the rubber liner is completely protected with an inert solid disk 0.05 mm. to 0.075 mm. in thickness. A suitable disk can be fabricated from a polytetrafluoroethylene resin.

Preparation of Apparatus—Clean all glassware thoroughly with chromic acid cleansing mixture and, if necessary, with hot nitric acid followed by prolonged rinsing with distilled water. Clean cutting devices by an appropriate method (*e.g.*, successive cleaning with acetone and methylene chloride prior to subdividing a specimen). Clean all other equipment by thorough detergent scrubbing and prolonged rinsing with distilled water.

Render containers and devices used for extraction and in transfer and administration of test material sterile and dry by a suitable process. If ethylene oxide is used as the sterilizing agent, then allow adequate time for complete degassing.

Procedure

Preparation of Sample—From a homogeneous plastic sample use a portion equivalent to 120 cm.^{2} when the thickness is 0.5 mm. or less, or 60 cm.^{2} when the thickness is greater than 0.5 mm.; subdivide into strips approximately 0.3 cm. wide and as near to 5 cm. in length as is practical. Remove particulate matter, such as lint and free particles, by treating each subdivided sample as follows: Transfer the subdivided sample to a clean 100-ml. glass-stoppered, graduated cylinder of Type I glass, and add about 70 ml. of water for injection. Agitate for about 30 seconds and drain off the water, repeat this step, and dry those pieces prepared for the extraction with cottonseed oil in an oven at a temperature not exceeding 50°. [NOTE: Do not clean the plastic with a dry or wet cloth or by rinsing or washing with an organic solvent, surfactant, etc.]

Extracts—Place two properly prepared *samples* of the plastic to be tested in separate extraction flasks, and add to each flask 20 ml. of the appropriate extracting medium. Repeat these directions for each extracting medium required for testing. Also prepare one 20-ml. blank of each medium for parallel injections and comparisons. Extract by heating in an autoclave at 121° for 60 minutes, in an oven at 70° for 24 hours, or at 50° for 72 hours. Allow adequate time for the liquid within the container to reach the extraction temperature.

[NOTE: The extraction conditions should not in any instance cause physical changes such as fusion or melting of the plastic pieces, which result in a decrease in the available surface area. A slight adherence of the pieces can be tolerated. Always add the cleaned pieces individually to the extracting medium. If culture tubes are used for autoclave extractions with cottonseed oil, seal screw caps adequately with pressure sensitive tape.]

Cool all containers at the end of the extraction period to about, but not below 22°. Agitate vigorously for several minutes, and then transfer each extract immediately to a dry, sterile container, and test within the following 24 hours. [NOTE: No extract should be stored at any time at temperatures below 22°.]

Acute Systemic Toxicity Test

Extracting Media—(1) Use Sodium chloride injection and (2) cottonseed oil.

Test Animal—Use healthy, not previously used albino mice weighing between 17 and 23 g. For each test group use only mice of the same source. Offer water and food, commonly used for laboratory animals and known as to composition, *ad libitum.*

Procedure—Inject into groups of 5 mice each the extract of the *sample* and the *blank* as outlined in Table I:

Table I. Injection Procedure

Extract or Blank	Dose per kg.	Route	Injection Rate (ml./sec.)
Sodium chloride injection	50 ml.	I.V.	0.1
Cottonseed oil	50 ml.	I.P.	. . .

Observe the animals immediately after injection, and at least at 24, 48, and 72 hours. If during the observation period all 5 of the animals treated with the extract of the *sample* show no significantly greater reaction than the animals treated with the *blank*, the *sample* meets the requirements of this test.

If any animals treated with the *sample* show only slight signs of toxicity, and not more than one animal shows gross symptoms of toxicity or death, repeat the test using groups of 10 mice. On the repeat test, all 10 animals treated with the *sample* should show no significant reaction above the *blank* animals during the observation period.

Eye Irritation Test

Extracting Media—Use (1) sodium chloride injection and (2) cottonseed oil.

Test Animal—Select healthy, albino rabbits with no visible eye irritation and not previously used for an eye irritation test. The animal facilities should be designed and maintained as to exclude sawdust, wood chips, or other extraneous materials that might produce eye irritation. Both eyes of the animals should be examined before testing and only those animals without eye defects or eye irritation should be used.

Procedure—Use three albino rabbits for each test. Restrain the animals firmly but gently until quiet. Gently pull the lower lid away from the eyeball to form a cup and instill about 0.2 ml. of the *blank* prepared as directed under *Acute Systemic Toxicity*. Hold the lid together for about 30 seconds. Instill into the other eye 0.2 ml. of the *sample* extract prepared as directed under *Acute Systemic Toxicity*. Examine the eyes at 24, 48 and 72-hour intervals. Examination is facilitated by the use of a binocular loupe and a hand slit-lamp.

The requirements of the test are met if the *sample* extract shows no significant irritation over the *blank* extract during the observation period. If irritation is observed in either eye of the rabbits, repeat the test using three additional rabbits. On the repeat test, all rabbits must meet the test requirement.

Chemical Test Procedures

The following tests are designed to determine the chemical properties of plastics of the specific extracts prepared from the plastic. It is essential not only to use the designated amount of the plastic, but also to make available the specified surface area for extraction.

Extracting Medium—Water for injection.

Apparatus

Oven—Use an oven, preferably a forced-draft model, which will maintain an operating temperature of 70° ± 1°.

Extraction Containers—Use *Extraction Containers* as described on page 845.

Preparation of Apparatus—Prepare the apparatus as described in the first paragraph under *Preparation of Apparatus*, page 845.

Procedure

Preparation of Sample—From a homogenous plastic sample, use a portion, for each 20.0 ml. of extracting medium, equivalent to 120 cm.^{2} when the thickness is 0.5 mm. or less, or 60 cm.^{2} when the thickness is greater than 0.5 mm.; subdivide into strips approximately 0.3 cm. wide and as near to 5 cm. in length as is practical. Transfer the subdivided sample to a 250-ml. glass-stoppered, graduated cylinder of Type I glass, and add about 150 ml. of water for injection. Agitate for about 30 seconds, drain off the water for injection, and repeat with a second washing.

Extracts—Transfer the prepared sample into a suitable extraction flask, and add the required amount of water for injection. Extract by heating in an oven at 70° for 24 hours. Allow adequate time for the liquid within the container to reach the extraction temperature. Cool, but not below 22°. Decant the extract immediately into a suitably cleaned container, and seal.

Blank—Use water for injection where a blank is specified in the following tests.

Nonvolatile Residue—Tare a suitable crucible, such as a fused silica crucible properly cleaned with acid, that has been dried to constant weight under the same conditions to be employed in the determination. Transfer 50.0 ml. of the *sample* extract in portions to the crucible, and evaporate the volatile matter on a steam bath. Dry the crucible at 105° to constant weight, cool, and weigh. (NOTE: If an oily residue is obtained, inspect the crucible repeatedly during the evaporation and drying period since such oils may creep along the walls of the crucible.) Perform a blank determination. The difference between the amounts, in mg., obtained from the *sample* and the *blank* is the amount, in mg., of *Nonvolatile Residue*.

Heavy Metals—Transfer 20 ml. of the *blank* and the *sample* extracts to separate color-comparison tubes. Transfer 2 ml. (1 part per million), 6 ml. (3 parts per million), and 10 ml. (5 parts per million) of *Standard Lead Solution* into separate color-comparison tubes, add 2 ml. of diluted acetic acid to each tube, and adjust the volume to 25 ml. with sterile water for injection. Add 10 ml. of freshly prepared hydrogen sulfide T.S. to each tube mix, allow to stand for 5 minutes, and view downward over a white surface. Determine the amount of heavy metals in the *blank* and in the *sample* by comparing the amount of darkening in each solution against that in the standard solution. If the *blank* or *sample* extract solution is darker than the highest standard, repeat the procedure using larger volumes of *Standard Lead Solution*. The heavy metals content is the difference between the *blank* and the *sample*.

POLAROGRAPHY

Polarography is an electrochemical method of analysis based on the measurement of the current flow resulting from the electrolysis of a solution at a microelectrode as a function of an applied voltage. The polarogram obtained by this measurement provides qualitative and quantitative information on electro-reducible and electro-oxidizable substances. The concentration range generally used for substances being analyzed is from $10^{-2}\,M$ to $10^{-5}\,M$.

In conventional polarography, the microelectrode is a dropping mercury electrode (D.M.E.) consisting of small reproducible drops of mercury flowing from the orifice of a capillary tube connected to a mercury reservoir. A saturated calomel electrode (S.C.E.) with a large surface area is the most commonly employed reference electrode. As the voltage applied to the cell increases, only a very small residual current flows until the substance under assay undergoes reduction or oxidation. Then the current increases, at first gradually, then almost linearly with voltage, and it gradually reaches a limiting value as is shown by the accompanying graph. On the initial rising portion of the polarographic wave, the increased flow of current results in a decrease in the concentration of the electroactive species at the electrode surface. As the voltage and current increase, the concentration of the reactive species decreases further to a minimal value at the electrode surface. The current is then limited by the rate at which the reacting species can diffuse thermally from the bulk of the solution to the surface of the microelectrode. The final current rise is caused by the reaction of the supporting electrolyte. This large concentration of electrolyte is inert within the potential range used in the analysis, and it prevents the reactive species from reaching the electrode by electrostatic attraction, thus assuring that the limiting current is diffusion-controlled.

Diffusion Current—The diffusion current (i_d) is a measure of the rate of diffusion of the electro-active species and is directly proportional to the concentration of the latter in the substance under assay. The limiting current, as is shown by the accompanying graph, is the sum of the residual current and the diffusion current. The residual current is subtracted from the limiting current to give the wave height. The linear relationship between the diffusion current and the concentration of electro-active species is shown by the Ilkovic equation,

$$i_d = 708nD^{1/2}Cm^{2/3}t^{1/6},$$

in which i_d is the maximum current in microamperes obtained just before the drop falls, n is the number of electrons required per molecule of electro-active substance, D is its diffusion coefficient in square centimeters per second, C is the concentration in millimoles per liter, m is the rate of mercury flow from the dropping mercury electrode in mg. per second, and t is the drop time in seconds.

According to the Ilkovic equation, the diffusion current should increase from a small value as the drop begins to form to a maximum value as the drop falls. The diffusion current will then drop abruptly to the low value and again increase in the same manner. By the use of a suitable recorder to measure the current, saw-toothed waves are obtained. Pen-and-ink recorders are sufficiently rapid to follow the current during the second half of the drop-life, but are too slow to respond to rapid current changes and do not show the current falling to a value near zero. Thus the average of the oscillations of the recorder pen is not equal to the average current during the life of the drop. The maximum of the oscillations should be determined as a measure of the current. For instruments using galvanometers to measure the current or pen recorders adjusted to simulate galvanometer recording, the saw-toothed waves correspond to oscillations about the average current. In this case, the average of the oscillations should be determined as a measure of the current. For polarograms obtained in this fashion, the i_d of the Ilkovic equation refers to the average current in microamperes during the life of the drop and the coefficient 708 is replaced by 607.

Control of the Diffusion Current—The Ilkovic equation suggests variables that must be controlled to ensure that the diffusion current is directly proportional to the concentration of electro-active material. At 25° the diffusion coefficients for aqueous solutions of many ions and organic molecules increase 1 to 2 percent per degree rise in temperature. Thus the temperature of the polarographic cell must be controlled to 0.5° at the generally accepted standard temperature of 25°. The quantities m and t depend upon the dimensions of the capillary and the height of the mercury column above the electrode. Although results obtained with different capillaries can be compared if the product $m^{2/3}t^{1/6}$ is known, it is advisable to use the same capillary with a constant head of mercury during a series of analyses. The diffusion current is proportional to the square root of the height of the mercury column. A mercury reservoir with a diameter greater than 4 cm. prevents any significant drop in the mercury level during a series of runs.

The capillary for the dropping mercury electrode has a bore of approximately 0.03 mm. to 0.05 mm. and a length of 6 cm. to 8 cm. The height of the mercury column, measured from the tip of the capillary to the top of the mercury pool, varies from 40 cm. to 80 cm. The exact length of the capillary and the height of the mercury column are determined by trial and error to give a drop-time of between 3 and 5 seconds at open circuit while immersed in the test solution.

Equipment is available which allows controlled drop-times of fractions of a second. As detail within a polarogram is related to the number of drops delivered during a given potential change, such short drop-times allow rapid recording of the polarogram.

The current flowing through the sample during the recording of a polarogram is in the microampere range. Thus, concentration changes in the bulk of the sample are negligible and several polarograms can be run on the same assay sample without significant differences.

Half-Wave Potential—The half-wave potential ($E_{1/2}$) occurs at the point on the polarogram one-half the distance between the residual current and the limiting current plateau. This potential is characteristic of the electro-active species and is independent of its concentration or the capillary used to obtain the wave. It is dependent upon the solution composition and may change with variations in the pH or in the solvent system or with the addition of complexing agents. The half-wave potential thus serves as one criterion for the identification of a sample.

The potential of the dropping mercury electrode is equal to the applied voltage versus the reference electrode after correction for the *iR* drop (that potential needed to pass the current, *i*, through the solution with a resistance, *R*). It is especially important to make this correction for nonaqueous solutions, which ordinarily possess high resistance, if an accurate potential for the D.M.E. is needed. Correction of the half-wave potential is not required for quantitative analysis. The expression "versus S.C.E." should follow potentials measured with the saturated calomel electrode to avoid confusion with potentials referred to other reference electrodes.

Removal of Dissolved Oxygen—Inasmuch as oxygen is reduced at the D.M.E. in two steps, first to hydrogen peroxide and then to water, it interferes where polarograms are to be made at potentials more negative than about 0 volt versus S.C.E. and must be removed. This may be accomplished by bubbling nitrogen through the solution under assay for 10 to 15 minutes immediately before recording the wave, the nitrogen first having been "conditioned" to minimize changes due to evaporation, by being passed through a separate portion of the solution.

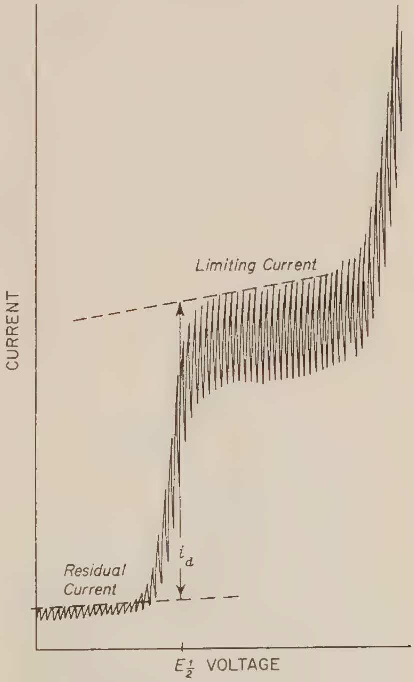
Before a polarogram is recorded, the flow of nitrogen must be switched to flow over the solution. It is necessary that the solution be quiet and vibration-free during the time the wave is recorded, to ensure that the current is diffusion-controlled.

Sodium bisulfite may be added to remove oxygen, provided that the reagent does not react with other components of the system.

Measurement of the Wave Height—To use a polarogram quantitatively, it is necessary to measure the height of the wave. Since this is a measure of the magnitude of the diffusion current, it must be measured vertically. To compensate for the residual current, the segment of the curve preceding the wave is extrapolated beyond the rise in the wave. For a well-formed wave where this extrapolation parallels the limiting current plateau, the measurement is unambiguous. For less well-defined waves the following procedure may be used unless otherwise directed in the individual monograph. Both the residual current and the limiting current are extrapolated with straight lines, as shown by the graph. The wave height is taken as the vertical distance between these lines measured at the half-wave potential.

Procedure—*Caution: Mercury is poisonous. Work in a well-ventilated laboratory, taking care to clean up any spilled mercury.*

Transfer a portion of the final dilution of the substance being assayed to a suitable polarographic cell immersed in a water bath regulated to 25 ± 0.5°. Pass a stream of nitrogen through the solution for 10 to 15 minutes to remove dissolved oxygen. Start the mercury dropping from the capillary, insert it into the sample solution, and adjust the height of the mercury reservoir. Switch the flow of nitrogen to pass over the surface of the solution, and record the polarogram over the potential range indicated in the individual monograph, using the appropriate recorder or galvanometer sensitivity to give a suitable wave. Measure the height of the wave, and unless otherwise directed in the monograph, compare this with a calibration curve obtained under the same conditions with the Reference Standard.



Typical Polarogram Showing Change in Current Flow with Increasing Potential

POWDER FINENESS

The fineness of powders in this National Formulary expressed in descriptive terms, is related to the number assigned to a standard sieve, as indicated in the accompanying table.

Sieves for National Formulary Testing

Nominal Dimensions of Standard Sieves (United States)

Number	Sieve Opening mm.	Sieve Opening μ	Permissible Variation in Average Opening, %	Permissible Variation in Maximum Opening, %	Nominal Wire Diameter, mm.
2	9.51	9510	±3	+ 6	2.27 ± 5%
4	4.76	4760	±3	+10	1.54 ± 5%
8	2.38	2380	±3	+10	1.00 ± 5%
10	2.00	2000	±3	+10	0.900 ± 5%
20	0.841	841	±5	+15	0.510 ± 5%
30	0.595	595	±5	+15	0.390 ± 10%
40	0.420	420	±5	+25	0.290 ± 10%
50	0.297	297	±5	+25	0.215 ± 10%
60	0.250	250	±5	+25	0.180 ± 10%
70	0.210	210	±5	+25	0.152 ± 10%
80	0.177	177	±6	+40	0.131 ± 10%
100	0.149	149	±6	+40	0.110 ± 10%
120	0.125	125	±6	+40	0.091 ± 10%
200	0.074	74	±7	+60	0.053 ± 15%

Classification of Powders by Fineness

Classification of Powder	Vegetable and Animal Drugs			Chemicals		
	Nominal Designation No.* of Powder	Fineness Limit† %	Fineness Limit† Sieve No.	Nominal Designation No.* of Powder	Fineness Limit† %	Fineness Limit† Sieve No.
Very coarse	8	20	60			
Coarse	20	40	60	20	60	40
Moderately coarse	40	40	80	40	60	60
Fine	60	40	100	80	100	80
Very fine	80	100	80	120	100	120

* All particles of the powder pass through a sieve of the nominal designation.

† Limit of the percentage that passes through a sieve of the size designated.

—Sieves for National Formulary testing are of wire cloth woven (not twilled) from bronze, or other suitable wire, and are not coated or plated. The accompanying table gives the nominal dimensions, permissible variations, and limits for woven wire cloth of standard sieves.

For details on the standardization of sieves, reference may be made to Specification E11-61 of the American Society for Testing and Materials.

Powdered Vegetable and Animal Drugs—In determining the powder fineness of a vegetable or animal drug, no portion of the drug may be rejected during milling or sifting unless specifically permitted in the individual monograph.

Method for Determining Uniformity of Fineness—For determining uniformity of degree of fineness of powdered drugs and chemicals, the following process may be used, employing standard testing sieves which meet the requirements set forth above.

For *very coarse, coarse,* and *moderately coarse powders,* place 5 to 50 g. of the powder to be tested upon the appropriate standard sieve having a close-fitting receiving pan and cover. Shake the sieve in a rotary horizontal direction and vertically by tapping on a hard surface for not less than 20 minutes or until sifting is practically complete. Weigh accurately the amount remaining on the sieve and in the receiving pan.

In the case of *fine* or *very fine powders,* proceed as for *coarse powders,* but shake the sieve for at least 30 minutes or until sifting is practically complete.

In the case of oily or other powders that tend to clog the openings, carefully brush the screen at intervals during the test. Break up lumps that form during the sifting. Do not increase the fineness of the powder during the testing.

The fineness of a powdered drug or chemical may be determined also by screening through standard sieves in a mechanical sieve shaker, which reproduces the circular and tapping motion given to testing sieves in hand sifting but with a uniform mechanical action, following the directions provided by the manufacturer of the shaker.

PRESSOR SUBSTANCES TEST

Standard Solution of Epinephrine—Weigh accurately 91 mg. of USP Epinephrine Bitartrate Reference Standard (equivalent to 50 mg. of $C_9H_{13}NO_3$, epinephrine base), previously dried in a vacuum desiccator for 18 hours, and transfer it to a 50-ml. volumetric flask with the aid of 10 ml. of freshly prepared sodium bisulfite solution (1 in 250). Add water to volume, and mix. Each ml. of this solution contains 1.0 mg. of $C_9H_{13}NO_3$ (epinephrine base). Preserve this solution in tight, hard-glass containers, and store in a refrigerator and protect from light. Use within 6 months. Do not use this solution if it shows any evidence of deterioration, such as change in color.

Standard Preparation—Dilute the *Standard Solution of Epinephrine* using sufficient saline T.S. so that, upon injection into the animal prepared for the test as directed herein, a dose of not less than 0.5 ml. and not more than 1.5 ml. produces a rise in blood pressure between 30 and 60 mm. of mercury.

The Animal—Using an anesthetic substance suitable for maintenance of a uniform level of blood pressure, anesthetize a dog of medium size deeply enough to prevent muscular movements such as shivering or twitching. Protect the animal from excessive loss of body heat by covering it or by applying heat. If preferable or if necessary, expose the trachea and insert a cannula so that the animal may receive artificial respiration during the course of the test. Expose a carotid artery, and insert a cannula connected to a mercury manometer arranged for making a continuous record of blood pressure. Expose a femoral vein, and inject into it 0.1 ml. per kg. of the dog's weight of an atropine sulfate solution (1 in 100). Consider the vagal receptor mechanism sufficiently paralyzed only if subsequent intravenous injections of 0.1 ml. per kg. of freshly prepared acetylcholine chloride solution (1 in 10,000) do not cause transient falls in blood pressure. If the vagal receptor mechanism is insufficiently paralyzed, inject doses of 0.05 ml. per kg. of the above-designated atropine sulfate solution until the paralysis is complete.

Procedure—Select a dose of the *Standard Preparation* which upon injection causes a rise in blood pressure between 30 and 60 mm. of mercury. Inject the selected dose at regular intervals of time which shall be not less than 5 minutes but long enough to allow the blood pressure to return to approximately its former level. When substantially uniform responses have been obtained from two or more injections of the same dose of the *Standard Preparation*, inject a dose of it which is expected to produce a rise in blood pressure approximately 20 percent greater than the average of the last two preceding doses. Use the animal for the test only if the responses to the same dose of the standard are uniform and between 30 and 60 mm. of mercury, and are significantly less than the response to the larger dose of the standard.

Following the time schedule established during the injection of the standard, inject alternately a suitable dose of the *Test Preparation* and the selected dose of the *Standard Preparation* to obtain a series of at least four responses. The average of the responses to the *Standard Preparation* in the series is not exceeded in height by the average of the responses to the dose of the *Test Preparation* which corresponds in amount to the limit on pressor activity specified in the individual monograph.

PYROGEN TEST

The pyrogen test is designed for products that can be tolerated by the test rabbit in a dose of 10 ml. per kg. injected intravenously within a period of not more than 2 minutes. For products that require preliminary preparation or are subject to special conditions of administration, follow the additional directions given in the individual monographs.

Temperature Recording—Use an accurate clinical thermometer which has been tested to determine the time necessary to reach the maximum reading, or any other temperature-recording device of equal sensitivity. Insert the temperature-sensing device into the rectum of the test animal to a depth of not less than 7.5 cm., and allow sufficient time to reach a maximum temperature, as previously determined, before taking the reading.

Test Animal—Use healthy, mature rabbits each weighing not less than 1.5 kg. House the animals individually in an area of uniform temperature (±3°[±5° F.]) and free from disturbances likely to excite them. Do not use animals for pyrogen tests more frequently than once every 48 hours, nor prior to 2 weeks following their having been given a test sample that was adjudged pyrogenic. Before using an animal that has not been used previously for a test, condition it by conducting a sham test as directed under *Procedure*, omitting the injection.

Procedure—Perform the test in an area where the animals are housed or under similar environmental conditions. During the test, withhold all food from the animals being used. Access to water may be allowed. Determine the "control temperature" of each animal. In any one test use only those animals the control temperatures of which do not deviate by more than 1° from each other, and do not use any animal with a temperature exceeding 39.8°. The control temperature recorded for each rabbit constitutes the temperature from which any subsequent rise following the injection of the material is calculated.

Render the syringes, needles, and glassware free from pyrogens by heating at 250° for not less than 30 minutes or by any other suitable method. Warm the product to be tested to approximately 37°.

Inject into an ear vein of each of three rabbits 10 ml. of the product per kg. of body weight within 30 minutes subsequent to the control temperature reading, unless otherwise specified in the individual monograph. Record the temperature at 1, 2, and 3 hours subsequent to the injection.

If no rabbit shows an individual rise in temperature of 0.6° or more above its respective control temperature, and if the sum of the three individual maximum temperature rises does not exceed 1.4°, the material under examination meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.6° or more, or if the sum of the three individual maximum temperature rises exceeds 1.4°, repeat the test using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.6° or more, and if the sum of the eight individual maximum temperature rises does not exceed 3.7°, the material under examination meets the requirements for the absence of pyrogens.

RADIOACTIVITY

Radioactive pharmaceuticals require specialized techniques in their handling and testing in order that correct results may be obtained and hazards to personnel be minimized. All operations should be carried out or supervised by personnel having had expert training in handling radioactive materials.

A *nuclide* is a species of atom characterized by the number of protons and neutrons in its nucleus. *Isotopes* are nuclides of the same atomic number (belonging to the same element), but of different atomic mass numbers. There are two classes of nuclides, *stable* and *unstable*, depending on the natural stability of the nucleus. *Unstable nuclides* are called *radioactive nuclides* or *radionuclides* since, when decay occurs, ionizing radiation in the form of alpha (α), beta (β), or gamma (γ) radiation, either singly or in combination, is emitted from the nucleus. The radiation consists of alpha particles, which are helium nuclei, positive and negative beta particles (positrons and negatrons), and gamma rays, which are high-energy photons. Individual radioactive nuclides differ from one another in the form of ionizing radiation emitted (α, β, or γ); the energy with which the radiation is ejected, usually expressed in millions of electron volts (Mev.); the rate of radioactive decay, usually expressed in terms of physical half-life ($T_{1/2}$); and the method of decay process, spoken of as the "decay scheme." The ionization induced by nuclear radiations forms the basis of their detection by instruments and produces radiation effects on biological systems.

The quantity of radioactivity is expressed in absolute units (total number of disintegrations or transformations per unit time) or comparative units (counts per unit time under specified conditions). The *curie* (Ci) and its subdivisions, *millicurie* (mCi) and *microcurie* (μCi) are the most commonly used absolute units: one Ci represents 3.700×10^{10} disintegrations or transformations per second and equals 10^3 mCi and $10^6\mu$Ci.

Production and Handling of Radioactive Pharmaceuticals—The following paragraphs concern special considerations applying to the NF monographs for radioactive drugs. Currently, the facilities for the production, use, and storage of radioactive pharmaceuticals are generally subject to licensing by the federal Atomic Energy Commission, although in certain cases this authority has been delegated to state agencies. The federal Department of Transportation regulates the conditions of shipment of radioactive materials. State and local agencies often have additional special regulations. Each producer or user must be thoroughly cognizant of the applicable regulations of the federal Food and Drug Administration and any additional requirements of the US Public Health Service, state, or local agencies pertaining to the articles concerned.

Carriers—The mass of radioactive material usually encountered in radioactive pharmaceuticals may be too small to be measured by ordinary chemical or physical methods. For example, the mass of ^{131}I having an activity of 100 millicuries may be as small as 8×10^{-7} g. Since such small amounts are not subject to the usual methods of separation and purification, a *carrier,* in the form of inactive material isotopic with the radionuclide, may be added during processing to permit ready handling. Amounts of such carriers must be sufficiently small as not to cause undesirable physiological effects. The term *carrier-free* refers to radioactive preparations in which no carrier is intentionally added during manufacturing or processing.

Preparation of Containers—Because of the extremely small concentrations found in some radioactive pharmaceuticals, special precautions often are necessary to avoid adsorption of radionuclides on the walls of the containers, including laboratory vessels.

Radionuclide Identification—It is recognized that the detection of small amounts of adventitious radionuclides presents technical difficulties. The statement, "Other radionuclides are absent," means that no foreign radiations are observed in spectra obtained during the expiry period of the preparation with the exception of those which may be accounted for by secondary radiation effects within the instrument used.

Expiration Date—The special nature of a radioactive pharmaceutical requires that it be assigned an expiration date, beyond which its continued use is not recommended. The expiry period so designated begins with the reference date of the radioactivity value (date of standardization) as it appears on the label and is usually stated in terms of months. For short-lived radionuclides (having a half-life of 60 days or less), the expiry period is approximately three half-lives. During the expiry period, the radioactivity will have decreased to the extent where insufficient radioactivity remains to serve the intended purpose or where the dose of active ingredient must be increased so much that undesirable physiological responses occur. For longer-lived radionuclides, the expiry period does not exceed six months. Use of products beyond their expiry periods is inadvisable, since unknown changes may take place in the formulation and the container as a result of the radioactivity and the storage conditions to which they have been subjected.

The expiry period is indicated on the label by the statement, "Do not use after —— month(s) from date of standardization." The date of standardization may be either the date of the actual assay for radioactivity or the date to which the value of the assay for radioactivity has been calculated by means of the half-life value.

The expiration-date requirements for the NIH-licensed products differ from those of the other radioactive pharmaceuticals, in that they are subject to an expiration date calculated from the time of actual preparation of the radioactive ingredient in accordance with the terms of the licensing agreement. For such products, the expiration date is indicated on the label by the specific month, day, and year.

Labeling—The labeling requirements stated in the individual monographs are intended to emphasize the special requirements for the articles concerned; for complete labeling requirements, the pertinent federal, state, and local regulations must be consulted.

Fundamental Decay Law—The rate of radioactive decay is characteristic for each individual radioactive nuclide. This rate of decay always follows an exponential course that permits expressing it in terms of the half-life. The *half-life* ($T_{1/2}$) is the time in which the radioactive intensity decreases to one-half the original value. The exponential decay curve is described mathematically by the equation

$$N = N_o e^{-\lambda t},$$

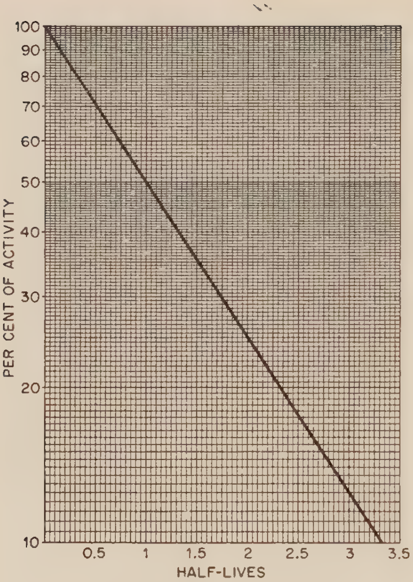
where N is the number of atoms at elapsed time t, N_o is the number of atoms when $t = 0$, and λ is the disintegration constant characteristic of each individual radionuclide. The half-life is related to the disintegration constant by the equation

$$T_{1/2} = \frac{0.693}{\lambda}.$$

Radioactive decay corrections are calculated from the exponential equation, or from decay tables, or by graphical means based on the half-life (see accompanying Master Decay Chart).

Detection and Measurement—Methods to be employed for detection and measurement of radioactivity are dependent upon the extent of energy dissipation and the penetration of the radiation. Radioactivity may be detected and/or measured by a number of different instruments the operation of which depends on the collection and measurement of ion pairs, the measurement of luminescence, or the measurement of the effect on a photographic emulsion.

In general, a counting assembly consists of a sensing unit and an electronic scaling device. The sensing unit may be a Geiger-Müller detector, a proportional



Master Decay Chart

counter, a solid-state detector, or a scintillation detector in which a multiplier phototube is coupled to a sodium iodide crystal activated with thallium. Geiger-Müller counters are used for detecting beta or gamma emitters; proportional counters are used for detecting alpha or beta emitters; and scintillation counters employing liquid or solid phosphors are used for detecting alpha, beta or gamma emitters. When the electronic scaling device or the scaler in a counting assembly is replaced with an electronic integrating device, the resultant assembly is a ratemeter. Ratemeters are used for the purpose of monitoring and surveying radioactivity and are somewhat less precise as measuring instruments than the counters. The *electrometer*, another instrument sometimes used, employs a charged quartz fiber that collects ions produced by a radioactive source with concomitant dissipation of the charge on the fiber and drift of the fiber across a scale. The rate of drift is a measure of the radioactivity. Ionization chambers, dosimeters and liquid scintillation counters are other forms of radiation measuring devices.

Radiation from a radioactive source is emitted in all directions. The procedure of standardization and measurement of beta emitters by means of a count of the emissions in all directions is known as 4π-counting, those procedures based on a count of the emissions in a solid angle of 180° are known as 2π-counting, and those based on a fraction of the emissions defined by the solid angle subtended from the detector to the source are known as counting by fixed geometry. Absolute beta counting by an end-window Geiger-Müller counter is an example of the latter. Calibration of radionuclides emitting both beta and gamma rays is by β-γ coincidence counting when these radiations are emitted in tandem or by scintillation spectrometry in which only the gamma rays are measured.

The construction and performance of instruments and accessory apparatus varies. The preparation of samples must be modified to obtain satisfactory results with a particular instrument. The operator must follow carefully the manufacturer's instructions for optimum instrument performance and substantiate results by careful examination of known samples.

Radioactivity due to materials of construction, to cosmic rays, and to spontaneous discharges in the atmosphere contributes what is known as the *background radioactivity*. All sample radioactivity measurements must be corrected by subtracting background radioactivity.

In the counting of samples at high activity levels, correction must be made also for coincidence loss.

Coincidence loss corrections must be made prior to the background correction.

A radioactivity count is a statistical value; *i.e.*, it is a measure of nuclear decay probabilities, and is not exactly constant over any given time interval. A sufficient number of counts must be determined to average out variations in the number of disintegrations per time interval. In general, at least 10,000 counts are necessary to obtain a standard deviation of 1 percent.

Absorption—Ionizing radiation is absorbed in the material surrounding the source of the radiation. Such absorption occurs in air, in sample coverings, in the window of the detection device, and in any special absorbers placed between the sample and the detector. Since alpha particles have a short range of penetration in matter, beta particles have a somewhat greater range, and gamma rays are deeply penetrating, identification of the type and energy of radiation emitted from a particular radionuclide may be determined by the use of absorbers of varying thicknesses.

The absorption coefficient (μ), expressed in cm.^{2}/mg., obtained through the use of aluminum absorbers of graduated thickness, is commonly determined to characterize the beta radiation emitted by a radioactive nuclide as by the following procedure. (For higher or lower energy sources, greater or lesser absorber thicknesses are necessary and will be specified as necessary in the individual monographs.)

Procedure—Place the radioactive substance, suitably mounted for counting, under a suitable counter. Make activity determinations individually and successively, using at least six different thicknesses of aluminum chosen from a range of 50 to 140 mg./cm.^{2} and a single absorber thicker than 800 mg./cm.^{2}. Obtain the net β-activity at the various absorbers used by subtracting the activity found with the 800 mg./cm.^{2} or greater absorber. Plot the logarithm of the net β-activity as a function of the total absorber thickness. The total absorber thickness is the thickness of the aluminum plus the thickness of the counter window (as stated by the manufacturer), plus the air equivalent thickness (the cm. distance of sample from the counter window × 1.205) all expressed in mg./cm.^{2}. An approximately straight line results.

Choose two of the absorber thicknesses that are 20 mg./cm.^{2} or more apart and that fall on the plot, and calculate the absorption coefficient by the equation

$$\mu = \frac{1}{t_2 - t_1} \ln \frac{N_{t_1}}{N_{t_2}}$$

where t_1 and t_2 represent the total absorber thicknesses greater than 10 mg./cm.^{2} and differing by at least 20 mg./cm.^{2}, t_2 being the thicker absorber, and N_{t_1} and N_{t_2} represent the net β-activity with t_1 and t_2 absorbers, respectively.

For characterization of the radionuclide, the absorption coefficient should be within ±5 percent of that found for a sample of the same radionuclide of known purity when determined concomitantly.

Activity at zero total absorber may be determined by means of plotting a curve identical to the one described for determination of the absorption coefficient and extrapolating the straight line plot to zero absorber thickness, taking into consideration the mg./cm.^{2} thickness of sample coverings, the air, and the counter window.

Scintillation Spectrometry—When the energy of beta or gamma radiation is dissipated within materials known as scintillators, light is produced in an amount proportional to the energy dissipated. This light may be measured by suitable means, and is proportional to the energy absorbed in the scintillator. Scanning of the output pulses with a suitable pulse-height analyzer results in an energy spectrum of the source. In general, beta scintillation spectra represent continuum of energies. Gamma-ray scintillation spectra show one or more sharp, characteristic photoelectric peaks, corresponding to the energies of the gamma radiation of the source, and thus are useful for identification purposes. These peaks are accompanied by other peaks or broad bands due to secondary effects of radiation on the scintillator or surrounding materials. Calibration of the instrument is achieved with the use of known samples of radioisotopes whose energy spectra have been characterized. The shape of the spectrum produced will vary with the instrument used, as a result of such factors as differences in shape and size of the crystal, shielding materials used, and types of discriminators employed in the pulse height analyzers. When using the spectrum for identification of radioisotopes it is therefore necessary to make the comparison of the spectrum with that of a known sample of the radionuclide obtained in the same instrument under identical conditions.

Radiation Shielding—Adequate shielding must be used to protect laboratory personnel from all ionizing radiation, and measuring instruments from background radiation.

Alpha and beta radiation is readily shielded because of its limited range of penetration. The range of alpha and beta particles varies inherently with their kinetic energy. The alpha particles are monoenergetic and have a range of a few centimeters in air. The absorption of beta particles, owing to their continuous energy spectrum and scattering, follows apparently an exponential function. The range of beta particles in air varies from centimeters to meters. Beta radiation produces an undesirable secondary radiation upon absorption by shielding materials. This radiation, known as Bremsstrahlung, resembles soft X-rays in its property of penetration. The higher the atomic number or density of the absorbing material, the greater the energy of the Bremsstrahlung produced. Elements of low atomic number produce low-energy Bremsstrahlung, which is readily absorbed; therefore, materials of low atomic number or of low density, such as aluminum, glass, or transparent plastic, are used to shield sources of beta radiation.

Gamma-ray radiation is deeply penetrating. Attenuation of gamma-ray radiation in matter is exponential and usually is expressed in terms of half-value layers. The half-value layer is the thickness of shielding material necessary to decrease the intensity of radiation to half its initial value. A shield of seven half-value thicknesses will reduce the radiation to less than 1 percent of its unshielded intensity of activity. Gamma-ray radiation is commonly shielded with lead.

Intensity of radiation is diminished according to the inverse square of the intervening distance between the source and the point of reference. Radioactive materials of multimillicurie strength can be handled safely in the laboratory by use of proper shielding and/or by arranging for the maximum practicable distance between the source and the operator by means of remote handling devices.

READILY CARBONIZABLE SUBSTANCES TEST

In tests for readily carbonizable substances, unless otherwise directed, add the specified quantity of the substance, finely powdered if in solid form, in small portions to the comparison container, which is made of colorless glass resistant to the action of sulfuric acid and contains the specified volume of sulfuric acid T.S., USP XVIII.

Stir the mixture with a glass rod until solution is complete, allow the solution to stand for 15 minutes, unless otherwise directed, and compare the color of the solution with that of the specified matching fluid in a comparison container which also is of colorless glass and has the same internal and cross-section dimensions, viewing the fluids transversely against a background of white porcelain or white glass.

When heat is directed in order to effect solution of the substance in the sulfuric acid T.S., mix the sample and the acid in a test tube, heat as directed, and transfer the solution to the comparison container for matching.

Special attention is directed to the importance of the concentration of sulfuric acid used in this test. The reagent of the required strength, *i.e.*, 95.0 ± 0.5 percent of H_2SO_4, is designated as a "Test Solution."

Matching Fluids—For purposes of comparison, a series of twenty matching fluids, each designated by a letter of the alphabet, is provided, the composition of each being as indicated in the accompanying table. To prepare the matching fluid required, pipet the prescribed volumes of the colorimetric test solutions (see *Colorimetric Solutions*, USP XVIII) and water into one of the matching containers, and mix the solution in the container.

Matching Fluids

Matching Fluid	Parts of Cobaltous Chloride C.S.	Parts of Ferric Chloride C.S.	Parts of Cupric Sulfate C.S.	Parts of Water
A	0.1	0.4	0.1	4.4
B	0.3	0.9	0.3	8.5
C	0.1	0.6	0.1	4.2
D	0.3	0.6	0.4	3.7
E	0.4	1.2	0.3	3.1
F	0.3	1.2	0.0	3.5
G	0.5	1.2	0.2	3.1
H	0.2	1.5	0.0	3.3
I	0.4	2.2	0.1	2.3
J	0.4	3.5	0.1	1.0
K	0.5	4.5	0.0	0.0
L	0.8	3.8	0.1	0.3
M	0.1	2.0	0.1	2.8
N	0.0	4.9	0.1	0.0
O	0.1	4.8	0.1	0.0
P	0.2	0.4	0.1	4.3
Q	0.2	0.3	0.1	4.4
R	0.3	0.4	0.2	4.1
S	0.2	0.1	0.0	4.7
T	0.5	0.5	0.4	3.6

REFERENCE STANDARDS, NF

NF Reference Standards are available to provide control standards required in certain National Formulary assays or tests, and as a service for use in other assays. They are not intended for drug use. They are prepared with the advice and technical assistance of members of the National Formulary Board, and advisory committees of specialists in the respective fields.

Unless otherwise directed, Reference Standards should be dried before use as directed in their labeling. If drying instructions are not provided in the labeling, and if drying is not specified in the particular test in the individual monograph, the Reference Standard may be used without drying, in which case the weight of the standard taken should be corrected for *Loss on drying* or *Water*, which are determined as directed in the monograph for the respective drug entity. Special directions may be given in a particular test when the Reference Standard is a hydrate.

If it is not feasible to determine the moisture content of the Reference Standard by the titrimetric method, page 900, and if the monograph for the respective drug entity does not contain a test for *Loss on drying*, the Reference Standard should be dried over a suitable desiccant in order to convert the weight of Standard taken to the anhydrous basis, unless otherwise directed.

Certain Reference Standards formerly required in tests and specifications appearing in previous editions of the National Formulary are available and will be supplied as long as stocks remain. Further information regarding these particular Reference Standards may be obtained from the NF office, at the address given below. Other Reference Standards required for National Formulary assays are supplied by the United States Pharmacopeia. Such Reference Standards may be obtained from USP Reference Standards, 4630 Montgomery Avenue, Bethesda, MD 20014.

NF Reference Standards are distributed by the authority of the National Formulary Board. The Reference Standards program is operated on a self-sustaining basis, and a price list is available upon request. NF Reference Standards may be obtained from National Formulary Reference Standards, American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, DC 20037. Those now available include the following:

Acetaminophen
Acetohexamide
Acetophenazine Maleate
Acetyldigitoxin
Acetyl Sulfisoxazole
Alverine Citrate
Ambenonium Chloride
Aminocaproic Acid
4-Amino-6-chloro-1,3-benzenedisulfonamide
2-Amino-5-chlorobenzophenone
4-Amino-6-chloro-N^3-methyl-*m*-benzenedisulfonamide
Amodiaquine Hydrochloride
Angiotensin Amide
Anisindione
Antazoline Phosphate
Anthralin
Antipyrine
Aprobarbital
Azure A
Bendroflumethiazide
Benzestrol
Benzocaine
Benzonatate
Benzphetamine Hydrochloride
Benzthiazide
1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride
Betamethasone
Betamethasone Acetate
Betamethasone Sodium Phosphate
Betamethasone Valerate
Biperiden
Biperiden Hydrochloride
Bisacodyl
Bromodiphenhydramine Hydrochloride
Brompheniramine Maleate
Butalbital
Butethamine Hydrochloride
Caffeine
Calcium Benzoylpas
Calcium Ipodate
Carbetapentane Citrate
Carbinoxamine Maleate
Carphenazine Maleate
Cetylpyridinium Chloride
Chloral Betaine
Chlorcyclizine Hydrochloride
Chlordiazepoxide
Chlormadinone Acetate
Chlormerodrin
7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide
Chloroprocaine Hydrochloride
Chlorothen Citrate
Chlorothiazide
Chlorotrianisene
Chlorprothixene
Chymotrypsin
Clidinium Bromide
Clofibrate
Cyclothiazide
Cycrimine Hydrochloride
Cyproheptadine Hydrochloride
Danthron
Denatonium Benzoate
Desipramine Hydrochloride
Desoxycorticosterone Pivalate
Dexbrompheniramine Maleate
Dexchlorpheniramine Maleate
Dextromethorphan Hydrobromide
Diazepam
Dicyclomine Hydrochloride
Dienestrol
Diethylpropion Hydrochloride
Dihydroxyaluminum Sodium Carbonate
Dimethindene Maleate
Dimethisoquin
Dimethisterone
Dimethyl Tubocurarine Iodide
Diphemanil Methylsulfate
Diphenadione
2,4-Disulfamyl-5-trifluoromethylaniline
Doxapram Hydrochloride
Dromostanolone Propionate
Dydrogesterone
Ephedrine Sulfate
Estradiol
Estradiol Benzoate
Estradiol Cypionate
Estradiol Dipropionate
Estrone
Ethamivan
Ethisterone
Fluocinolone Acetonide
Fluorometholone
Fluphenazine Enanthate Dihydrochloride
Fluphenazine Hydrochloride
Fluprednisolone
Flurandrenolide
Furazolidone
Gitalin
Glutethimide
Glyceryl Guaiacolate
Glycopyrrolate
Guaiacol
Haloperidol
Hexylcaine Hydrochloride
Homatropine Methylbromide
Hyaluronidase
Hydralazine Hydrochloride
Hydroflumethiazide
Hydroquinone
3-Hydroxy-1-methylquinuclidinium Bromide
Hydroxyzine Hydrochloride
Hydroxyzine Pamoate
Iminodibenzyl
Indomethacin
Isocarboxazid
Isopropamide Iodide
Isoxsuprine Hydrochloride
Lanatoside C
Levopropoxyphene Napsylate
Menadione
Mepenzolate Bromide
Mepivacaine Hydrochloride
Metabutethamine Hydrochloride
Methandrostenolone
Methantheline Bromide
Methapyrilene Hydrochloride
Metharbital
Methdilazine
Methdilazine Hydrochloride
Methocarbamol
Methohexital
Methotrimeprazine
Methoxyflurane
Methscopolamine Bromide
Methsuximide
Methyclothiazide
Methyl 5-Methyl-3-isoxazolecarboxylate
Methylprednisolone
Methylprednisolone Acetate
Methylprednisolone Sodium Succinate
Methyltestosterone
Methyprylon

Methysergide Maleate
Nalidixic Acid
Nandrolone Decanoate
Nandrolone Phenpropionate
Naphazoline Hydrochloride
Niacin
Nialamide
Nifuroxime
Nitrofurazone
5-Nitro-2-furfuraldazine
Norethandrolone
Norethindrone Acetate
Nortriptyline Hydrochloride
Nylidrin Hydrochloride
Orphenadrine Citrate
Oxandrolone
Oxazepam
Oxymetazoline Hydrochloride
Oxymetholone
Oxyphenbutazone
Oxyphencyclimine Hydrochloride
Pancreatin
Paramethasone Acetate
Pargyline Hydrochloride
Pentazocine
Penthienate Bromide
Pentylenetetrazol
Perphenazine
Phenazopyridine Hydrochloride
Phenindamine Tartrate
Phenmetrazine Hydrochloride
Phenprocoumon
Phensuximide
cis-2-Phenylcyclopropylamine Sulfate
Pipobroman
Polythiazide
Potassium Gluconate
Potassium Guaiacolsulfonate
Potato Starch
Pramoxine Hydrochloride
Prednisolone Succinate
Prilocaine Hydrochloride
Progesterone
Promazine Hydrochloride
Propiomazine Hydrochloride
Propoxycaine Hydrochloride
Pseudoephedrine Hydrochloride
Pyrilamine Maleate
Pyrrobutamine Phosphate
Quinine Dihydrochloride
3-Quinuclidinyl Benzilate
Rauwolfia Serpentina
Rescinnamine
Saccharin
Salicylamide
Sitosterols
Sodium Butabarbital
Sodium Fluoride
Sodium Ipodate
Stanozolol
Sulfadimethoxine
Sulfaethidole
Sulfamethoxazole
Syrosingopine
Terpin Hydrate
Testosterone
Tetrahydrozoline Hydrochloride
Thiethylperazine Maleate
Thihexinol Methylbromide
Thimerosal
Thioguanine
Thiopropazate Hydrochloride
Tranylcypromine Sulfate
Triacetin
Triamcinolone Diacetate
Trichlormethiazide
Triclobisonium Chloride
Tridihexethyl Chloride
Triethylenemelamine
Trifluoperazine Hydrochloride
Triflupromazine Hydrochloride
Trimeprazine Tartrate
Trimethobenzamide Hydrochloride
Trioxsalen
Triprolidine Hydrochloride
Tromethamine
Trypsin Crystallized
Tuaminoheptane Sulfate
Tybamate
Tyrosine
Urethan
Valethamate Bromide
Vinbarbital
Xylometazoline Hydrochloride

REFRACTIVE INDEX

The refractive index (n) of a substance is the ratio of the velocity of light in air to the velocity of light in the substance. It is valuable in the identification of substances and the detection of impurities.

Although the standard temperature for official measurements is 25°, many of the refractive index specifications in the individual monographs call for determining this value at 20°. The temperature should be carefully adjusted and maintained, since the refractive index varies with temperature.

The values for refractive index given in this National Formulary are for the D line of sodium (589 $m\mu$). Most instruments available are designed for use with white light, but are calibrated to give the refractive index in terms of the D line of sodium light.

The Abbé refractometer measures the range of refractive index for those National Formulary materials for which such values are given. Other refractometers of equal or greater accuracy may be employed.

RESIDUE ON IGNITION

Weigh accurately 1 to 2 g. of the substance, or the amount specified in the individual monograph, in a suitable tared crucible. Ignite, gently at first, until the substance is thoroughly charred, cool, then, unless otherwise directed in the individual monograph, moisten the residue with 1 ml. of sulfuric acid, and ignite at 800 ± 25° until the carbon is consumed. Cool in a desiccator, weigh, and calculate the percentage of residue. If the amount of residue so obtained exceeds the limit specified in the individual monograph, ignite to constant weight, and again calculate the percentage of residue. Conduct the ignition in a place protected from air currents.

RIBOFLAVIN ASSAY

The following procedure is suitable for preparations in which riboflavin is a constituent of a mixture of several ingredients. In employing it, keep the pH of solutions below 7.0, and protect the solutions from direct sunlight at all stages.

Standard Riboflavin Stock Solution—To 50.0 mg. of USP Riboflavin Reference Standard, previously dried at 105° for 2 hours and stored protected from light in a desiccator over phosphorus pentoxide, add about 300 ml. of 0.02 *N* acetic acid, and heat the mixture on a steam bath, with frequent agitation, until the riboflavin has dissolved. Then cool, and add 0.02 *N* acetic acid to make 500 ml. Store under toluene in a refrigerator.

Dilute an accurately measured portion of this solution, using 0.02 *N* acetic acid, to a concentration of 10.0 mcg. of the dried USP Riboflavin Reference Standard per ml., to obtain the *Standard Riboflavin Stock Solution*. Store under toluene in a refrigerator.

Standard Preparation—Dilute 10.0 ml. of *Standard Riboflavin Stock Solution* with water to make 100.0 ml. Each ml. represents 1.0 mcg. of USP Riboflavin Reference Standard. Prepare fresh *Standard Preparation* for each assay.

Assay Preparation—Place an amount of the material to be assayed in a flask of suitable size and add a volume of 0.1 *N* hydrochloric acid equal in ml. to not less than 10 times the dry weight of the material in g., but the resulting solution shall contain not more than 100.0 mcg. of riboflavin in each ml. If the material is not readily soluble, comminute it so that it may be evenly dispersed in the liquid. Then agitate vigorously, and wash down the sides of the flask with 0.1 *N* hydrochloric acid.

Heat the mixture in an autoclave at 121° to 123° for 30 minutes, and cool. If clumping occurs, agitate the mixture until the particles are evenly dispersed. Adjust the mixture, with vigorous agitation, to a pH of 6.0 to 6.5 with sodium hydroxide solution† then add hydrochloric acid solution† immediately until no further precipitation occurs (usually at a pH of approximately 4.5, the isoelectric point of many of the proteins present). Dilute the mixture with water to make a measured volume that contains more than 0.1 mcg. of riboflavin in each ml., and filter through paper known not to adsorb riboflavin. To an aliquot of the filtrate add, with vigorous agitation, sodium hydroxide solution† to produce a pH of 6.6 to 6.8, dilute the solution with water to make a final measured volume that contains approximately 0.1 mcg. of riboflavin in each ml., and if cloudiness occurs, filter again.

Procedure—To each of four or more tubes (or reaction vessels) add 10.0 ml. of the *Assay Preparation*. To each of two or more of these tubes add 1.0 ml. of the *Standard Preparation* and mix, and to each of two or more of the remaining tubes add 1.0 ml. of water, and mix. To each tube add 1.0 ml. of glacial acetic acid, mix, then add, with mixing, 0.5 ml. of potassium permanganate solution (1 in 25), and allow to stand for 2 minutes. To each tube add, with mixing, 0.5 ml. of hydrogen peroxide solution, whereupon the permanganate color is destroyed within 10 seconds. Shake the tubes vigorously until excess oxygen is expelled. Remove any gas bubbles remaining on the sides of the tubes after foaming has ceased, by tipping the tubes so that the solution flows slowly from end to end.

In a suitable fluorophotometer, having an input filter of narrow transmittance range with a maximum at about 440 mμ and an output filter of narrow transmittance range with a maximum at about 565 mμ, measure the fluorescence of all tubes, designating the average reading from the tubes containing only the *Assay Preparation* as I_U and the average from the tubes containing both the *Assay Preparation* and the *Standard Preparation* as I_S. Then to each of one or more tubes of each kind add, with mixing, 20 mg. of sodium hydrosulfite, and within 5 seconds again measure the fluorescence, designating the average reading as I_B.

Calculation—Calculate the quantity, in mg. on the dried basis, of $C_{17}H_{20}N_4O_6$ in each ml. of the *Assay Preparation* taken by the formula $0.0001\ (I_U - I_B)/(I_S - I_U)$. Calculate the quantity, in mg. on the dried basis, of $C_{17}H_{20}N_4O_6$ in each capsule or tablet.

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† The concentrations of the hydrochloric acid and sodium hydroxide solutions used are not stated in each instance because these concentrations may be varied depending upon the amount of material taken for assay, volume of test solution, and buffering effect of material.

ROSIN TEST

In testing for rosin as an adulterant in resins, gum resins, and balsams, unless otherwise directed, place in a small mortar 1 g. of the substance, powdered or crushed if necessary, and add 10 ml. of solvent hexane. Triturate well for 1 or 2 minutes, filter into a test tube, and to the filtrate add 10 ml. of a fresh cupric acetate solution (1 in 200). Shake well, and allow the liquids to separate: the hexane layer does not show a green color.

RUBBER CLOSURES FOR INJECTIONS

Rubber may be of synthetic or natural origin. It is generally a complex mixture of many ingredients. These include the basic polymer, fillers, accelerators, vulcanizing agents, pigments, etc. The properties of the rubber closure are not only dependent upon these ingredients, but also on the processing procedure, such as mixing, milling, dusting agents used, molding, curing, etc.

Factors such as cleansing procedures, contacting media and conditions of storage may also affect the suitability of a rubber closure for a specific use. Evaluation of such factors should be made by appropriate additional specific tests to determine the suitability of a rubber closure for its intended use.

Definitions—For the purpose of this chapter these definitions apply: A *rubber closure* is a device which is, or may be, in direct contact with the drug. The *sample* is the rubber specimen under test or the extract prepared from such a specimen. A *blank* consists of the same quantities of the same extracting medium used for the extraction of the specimen under test, treated in the same manner as the extracting medium containing the specimen under test.

Biological Test Procedures

The following tests are designed to determine the biological response of animals to rubber closures by the injection of specific extracts prepared from the rubber closure. It is essential not only to use the designated number of rubber closures, but also to make available the specific surface area for extraction. Also it is essential to exercise care in the preparation of the materials to be injected to prevent contamination with microorganisms and other foreign matter.

Extraction Media—Sodium chloride injection; cottonseed oil; polyethylene glycol 400.

Apparatus

Autoclave—Employ an autoclave capable of maintaining a temperature of 121 ± 0.5°, equipped with a thermometer, a pressure gauge, a rack adequate to accommodate the test containers above the water level, and a water cooling system which will allow for cooling of the test containers.

Oven—Use an oven, preferably a forced-draft model, which will maintain operating temperatures in the range of 50° to 70° within ±1°.

Extraction Containers—Use only containers, such as ampuls or screw-cap culture test tubes, or their equivalent, of Type I glass. If used, culture test tubes, or their equivalent, are closed with a screw cap having a suitable rubber liner. The exposed surface of the rubber liner is completely protected with an inert solid disk 0.05 mm. to 0.075 mm. in thickness. A suitable disk can be fabricated from a polytetrafluoroethylene resin.

Preparation of Apparatus—Clean all glassware thoroughly with chromic acid cleansing mixture and, if necessary, with hot nitric acid followed by prolonged rinsing with sterile water for injection. Render containers and devices used for extraction, transfer, or administration of test material sterile and dry by a suitable process. If ethylene oxide is used as the sterilizing agent, allow at least 48 hours for complete degassing.

Procedure

Preparation of Sample—Place a selected number of intact rubber closures in each extraction container, add 50 ml. of sterile water for injection, cap, and agitate for 2 to 3 minutes. Decant, using a stainless steel screen to hold the closures in the tubes. Repeat this step. Treat all *blank* tubes in a similar manner. Remove the caps and place the tubes containing the *sample* and *blank* and the caps in an oven at a temperature of about 50° and allow to dry. Do not dry for more than 16 hours.

Extracts—Place two properly prepared *samples* to be tested in separate extraction tubes, and add to each tube a sufficient quantity of the appropriate extractant (1 ml. of extractant per 1.25 ± 0.10 cm.^{2}). Extract by heating in an autoclave at 121° for 60 minutes. Allow adequate time for the liquid within the container to reach the extraction temperature.

Cool all containers at the end of the extraction to about, but not below 22°. [Note—No extract should be stored at any time at temperatures below 22°.] Agitate vigorously for several minutes and then transfer aseptically each extract immediately to a dry, sterile container, and test within the following 24 hours.

Acute Systemic Toxicity and Intracutaneous Reactivity Tests

The acute systemic toxicity test and the intracutaneous reactivity test are designed for the evaluation of the extracts of rubber closures. Of importance is the contact of the extracting medium with the total surface area of the rubber closures and the time and temperature during extraction, the proper cooling, agitation and decanting process, as well as the aseptic handling and storage of the extracts following extraction. [Note—Each extract must be agitated vigorously prior to withdrawal of each injection dose to ensure even distribution of the extracted matter.]

Acute Systemic Toxicity Test

Test animal—Use healthy, not previously used albino mice weighing between

17 and 23 g. For each test group use only mice of the same source. Offer water and food, commonly used for laboratory animals and known as to composition, *ad libitum.*

Procedure—Inject each of the five mice in a test group with the sample or the *blank* as outlined in Table I.

Table I. Injection Procedure

Extract or Blank	Dose per kg.	Route*	Injection Rate (ml./second)
Sodium chloride injection	50 ml.	I.V.	0.1
Polyethylene glycol 400	10 g.	I.P.	. . .
Cottonseed oil	50 ml.	I.P.	. . .

* I.V.—Intravenous; I.P.—Intraperitoneal.

Observe the animals immediately after injection, again 4 hours after injection, and then at least at 24, 48, and 72 hours. If during the observation period none of the animals treated with the extract of the *sample* show a significantly greater reaction than the animals treated with the *blank,* the *sample* meets the requirements of this test. If any animals treated with the *sample* show only slight signs of toxicity, and not more than 1 animal shows gross symptoms of toxicity or death, repeat the test using groups of 10 mice. On the repeat test, all 10 animals treated with the *sample* should show no significant reaction above the *blank* animals during the observation period.

Intracutaneous Reactivity Test

Test Animal—Select healthy, thin-skinned albino rabbits not previously used for any test, whose fur can be clipped closely and whose skin is free from mechanical irritation or trauma. In handling the animals, avoid touching the injection sites during observation periods.

Procedure—On the day of the test, closely clip the fur on the animal's back on both sides of the spinal column over a sufficiently large test area. Avoid mechanical irritation and trauma. Remove loose hair by means of vacuum. If necessary, swab the skin slightly with diluted alcohol and dry the skin prior to injection. For each *sample* use two animals and inject each intracutaneously, using one side of the animal for the *sample* and the other side for the *blank,* as outlined in Table II.

Table II. Intracutaneous Injection Procedure

Extract or Blank	Number of Sites (per animal)	Dose* (ml./site)
Sample	10	0.2
Blank	5	0.2

* Dilute extracts and blanks prepared with polyethylene glycol 400 with sodium chloride injection to 24 mg. per 0.2 ml.

Examine injection sites for evidence of any tissue reaction such as erythema, edema, and necrosis. Swab the skin slightly, if necessary, with diluted alcohol to facilitate reading of injection sites. Observe all animals at 24, 48, and 72 hours after injection. Re-clip the fur as necessary during the observation period.

If each animal at any observation period shows an average reaction to the *sample* which is not significantly greater than to the *blank,* the *sample* meets the requirements of this test. If at any observation period the average reaction to the *sample* is questionably greater than the average reaction to the *blank,* repeat the test using 3 additional rabbits. On the repeat test, the average reaction to the *sample* in any of the 3 animals should not be significantly greater than the *blank.*

Physicochemical Test Procedures

The following tests are designed to determine such physical and chemical properties of rubber closures and their extracts as are specified in individual monographs. Since the tests are based on the extraction of the rubber, it is essential that the designated amount of the rubber is used. In each case, the specified surface area must be available for extraction at the designated temperature. The test methods are devised to detect the majority of expected variations.

Extraction Medium—Sterile water for injection.

Apparatus

Autoclave—An autoclave capable of maintaining a temperature of 121 ± 0.5°, equipped with a thermometer, a pressure gauge, and a rack adequate to accommodate the test containers above the water level.

Oven—Use an oven, preferably force-draft model, which will maintain an operating temperature at 105°.

Procedure

Preparation of Sample—Place a selected number of rubber closures in a suitable extraction container. Add 300 ml. of sterile water for injection, cover each flask with a suitable inverted beaker, and autoclave at 121 ± 0.5° for 30 minutes. [Note—Adjust so that the temperature rises rapidly, preferably within 2 to 5 minutes.] Decant, using a stainless steel screen to hold the closures in the containers. Rinse with 100 ml. of sterile water for injection, gently swirl, and discard the rinsings. Repeat with a second 100-ml. portion of sterile water for injection.

Treat all *blank* containers in a similar manner.

Extracts—Place a properly prepared sample in a suitable container, and add a sufficient quantity of sterile water for injection (2 ml. of extractant per 1 ± 0.10 cm^2.). Cover with a suitable inverted beaker, and extract by heating in an autoclave at 121° for 2 hours, allowing adequate time for the liquid within the container to reach the extraction temperature. Allow the autoclave to cool rapidly, and cool to room temperature. Treat the *blank* container in a similar manner.

Turbidity—Agitate the container and transfer a sufficient quantity to a cell. Measure the turbidity in a suitable nephelometer (see page 873), against fixed reproducible standards.* The turbidity is the difference between the blank and the sample expressed in Nephelos units, an arbitrary linear numerical scale expressing a haze range from absolute clarity to the zone of turbidity.

Reducing Agents—Agitate the container, transfer 50 ml. of *sample* to a suitable container, and titrate with 0.01 *N* iodine, using starch T.S. as the indicator. Treat the *blank* in a similar manner. The difference between the *blank* and the *sample* titration is expressed in ml. of 0.01 *N* iodine.

Heavy Metals—Transfer 20 ml. of the *blank* and the *sample* extracts to separate color-comparison tubes. Transfer 2 ml., 6 ml., and 10 ml. of Standard Lead Solution into separate color-comparison tubes, add 2 ml. of diluted acetic acid to each tube, and adjust the volume to 25 ml. with sterile water for injection. Add 10 ml. of freshly prepared hydrogen sulfide T.S. to each tube, mix, allow to stand for 5 minutes, and view downward over a white surface. Determine the amount of heavy metals in the *blank* and in the *sample*. The heavy metals content is the difference between the *blank* and the *sample*.

pH Change—Determine the pH of the *blank* and the *sample* potentiometrically. The pH change is the difference between the *blank* and the *sample*.

Total Extractables—Agitate the containers, and transfer 100-ml. aliquots of the *blank* and the *sample* into separate tared evaporating dishes. Evaporate to dryness on a steam bath or in an oven at 100°, dry at 105° for 1 hour, cool in a desiccator, and weigh. Calculate the total extractables, in mg., by the formula: $(V/100) \times (sample - blank) \times 3$, in which V is the total extract volume, in ml.

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* A suitable Nephelos Standard is available from Coleman Instruments, Inc., Maywood, IL 60153.

SALMONELLA TEST*

Screening tests for Salmonella contamination are highly exacting and should be conducted by personnel having had expert training and extensive experience in microbiological testing in general.

Media†

Prepare media according to the following formulas and directions. Adjust the solutions with either 1 *N* sodium hydroxide or 1 *N* hydrochloric acid as required so that, after sterilization, the pH is within ±0.1 unit of the value indicated in the formula. Dehydrated mixtures may be used provided that, when reconstituted as directed in the labeling, they have the same ingredients as, and yield media comparable to, those obtained from the formulas given herein. Unless otherwise specified, sterilize all test media after constitution in an autoclave for 15 minutes at 121° (15 pounds pressure).

I. Lactose Broth

Beef Extract	3.0 g.
Peptone or Gelatin Hydrolysate	5.0 g.
Lactose	5.0 g.
Water	1000 ml.

Dissolve the ingredients in the water, and adjust the pH to 6.8.

II. Selenite-Cystine Broth

Tryptone or Polypeptone	5.0 g.
Lactose	4.0 g.
Sodium Phosphate, Dibasic	10.0 g.
Sodium Selenite	4.0 g.
Cystine	10 mg.
Water	1000 ml.

Dissolve the ingredients in the water, adjust the pH to 7.0, and steam for 15 minutes. *Do not autoclave.*

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* Note—All temperatures herein specified are in centigrade (Celsius) degrees and, with respect to autoclaves, generally mean the exhaust line temperatures.

† Peptone, Tryptone, Proteose Peptone, and Proteose Peptone No. 3 are available from Difco Laboratories, Detroit, MI 48201; Gelatin Hydrolysate (Gelsate) and Polypeptone are available from Baltimore Biological Laboratory (BBL), Division of Bioquest, Cockeysville, MD 21030.

III. Triple Sugar-Iron-Agar (TSI)

Beef Extract	3.0 g.
Yeast Extract	3.0 g.
Peptone	15.0 g.
Proteose Peptone	5.0 g.
[Note: The above four ingredients may be replaced with 20 g. of Polypeptone.]	
Lactose	10.0 g.
Saccharose	10.0 g.
Dextrose	1.0 g.
Ferrous Sulfate	200 mg.
Sodium Chloride	5.0 g.
Sodium Thiosulfate	300 mg.
Agar	13.0 g.
Phenol Red	24 mg.
Water	1000 ml.

Mix the ingredients with the water, and heat to boiling to dissolve. Adjust the pH to 7.3. Dispense into tubes. After sterilization, slant to give a generous butt.

IV. Brilliant Green Agar (BG)

Yeast Extract	3.0 g.
Proteose Peptone No. 3 or Polypeptone	10.0 g.
Sodium Chloride	5.0 g.
Lactose	10.0 g.
Saccharose	10.0 g.
Phenol Red	80 mg.
Brilliant Green	12.5 mg.
Agar	20.0 g.
Water	1000 ml.

Mix the ingredients with the water, boil to dissolve, and adjust the pH to 6.9. Dispense into bottles or flasks. Sterilize at 121° for 12 minutes.

V. Salmonella-Shigella Agar Modified (SSM)

Beef Extract	5.0 g.
Proteose Peptone or Polypeptone	5.0 g.
Lactose	10.0 g.
Bile Salts	8.5 g.
Sodium Citrate	8.5 g.
Sodium Thiosulfate	8.5 g.
Ferric Citrate	1.0 g.
Agar	20.0 g.
Saccharose	5.0 g.
Brilliant Green	330 mcg.
Neutral Red	25 mg.
Water	1000 ml.

Mix the ingredients with the water, heat to boiling to dissolve, and adjust the pH to 7.0. *Do not autoclave.* Pour into plates, and permit to dry with tilted covers.

VI. Tetrathionate Broth

Proteose Peptone or Polypeptone	5.0 g.
Bile Salts	1.0 g.
Calcium Carbonate	10.0 g.
Sodium Thiosulfate	30.0 g.
Water	1000 ml.

Mix the ingredients with the water, heat to boiling to dissolve, and cool to below 45°. Add 20 ml. of iodine solution prepared by dissolving 5 g. of potassium iodide in 5 ml. of water, adding 6 g. of iodine, shaking to dissolve, and adding 15 ml. of water. Add 1 ml. of a 1 in 1000 solution of brilliant green, and mix. Do not heat after the addition of the iodine solution. Dispense into sterile containers, and use on the day of preparation. (The basal medium without the iodine solution may be sterilized by autoclaving and stored indefinitely in screw-capped flasks.)

VII. XL Agar Modified

Yeast Extract	3.0 g.
L-Lysine	5.0 g.
Xylose	3.75 g.
Lactose	7.5 g.
Saccharose	7.5 g.
Sodium Chloride	5.0 g.
Phenol Red	80 mg.
Agar	20.0 g.
Water	1000 ml.

Mix the ingredients with the water, and heat to boiling to dissolve. Cool to 55° to 60° after autoclaving, and then add aseptically 20 ml. of a sterile aqueous solution containing 34 percent of sodium thiosulfate and 4 percent of ferric ammonium citrate. Sterilize the solution by membrane filtration. Adjust the pH to 6.9, mix, and dispense into plates.

VIII. Bismuth Sulfite Agar

Beef Extract	5.0 g.
Peptone or Polypeptone	10.0 g.
Dextrose	5.0 g.
Disodium Phosphate	4.0 g.
Ferrous Sulfate	300 mg.
Bismuth Sulfite Indicator	8.0 g.
Agar	20.0 g.
Brilliant Green	25 mg.
Water	1000 ml.

Mix the ingredients with the water, boil for 1 minute, and adjust the pH to 7.7. A characteristic precipitate will form on boiling. Dispense into plates. *Do not autoclave.*

Sampling

Analyze all samples as quickly as possible after collection. Refrigerate all samples that are moist, *e.g.*, swabs, bile, glands, etc., immediately after collection.

Make all indicated pH adjustments with 1 *N* sodium hydroxide or 1 *N* hydrochloric acid, and use narrow-range pH indicator paper in determining the pH.

Powders, Tablets, Filled Gelatin Capsules—Weigh 25 g. of sample into a sterile wide-mouth, screw-capped 500-ml. jar. Add 225 ml. of Lactose Broth. At this point, samples of filled gelatin capsules should be heated for about 25 minutes in a 42–45° water bath to dissolve the capsules. Shake all samples vigorously, and check the pH. If below 6.0 or over 7.1, adjust the pH to 7.0. Loosen the cap to permit gas to escape. Incubate at 35° for 24 to 48 hours.

Greasy, Oily, or Fatty Samples; Animal Feed—Weigh 25 g. of sample into a sterile wide-mouth, screw-capped 500-ml. jar. Add 225 ml. of Lactose Broth containing sterile 1 percent polysorbate 80 or other suitable anionic wetting agent. Shake well, and check the pH. If below 6.0 or over 7.1, adjust the pH to 7.0. Loosen the cap to permit gas to escape. Incubate at 35°, for 24 to 48 hours.

Swabs; Environmental Samples—Place the sample in 25 ml. of Lactose Broth containing 1 percent sterile polysorbate 80 or other suitable anionic wetting agent. Shake well, and check the pH. If below 6.0 or over 7.1, adjust the pH to 7.0. Loosen the cap to permit gas to escape. Incubate at 35° for 24 to 48 hours.

Frozen Animal Glands—Weigh 25 g. of sample into a sterile blending jar. Add 225 ml. of Selenite-Cystine Broth, and blend for 2 minutes at low speed. Aseptically transfer to a sterile wide-mouth, screw-cap 500-ml. jar. Loosen the cap to permit gas to escape. Incubate at 35° for 18 to 24 hours.

Liquid Products; Water; Bile—Using a sterile membrane filtration apparatus, filter appropriate dilutions and amounts of sample so that there are approximately 10 to 200 organisms on the filter pad. After filtering, place the pad on a Brilliant Green Agar plate. Incubate at 35° for 48 hours. Pick colonies to Triple Sugar-Iron-Agar slants and to Selenite-Cystine Broth.

Gelatin—Weigh 25 g. into a sterile wide-mouth, screw-capped 500-ml. jar. Add 225 ml. of sterile Lactose Broth, and heat for about 25 minutes in a 42–45° water bath to dissolve the gelatin. Shake vigorously. Loosen the cap to permit gas to escape. Incubate at 35° for 24 to 48 hours.

Thyroid-Related Products (Powder or Tablets)—Weigh 25 g. of the dry product into a sterile wide-mouth, screw-capped 500-ml. jar. Add 15 to 20 ml. of sterile Lactose Broth, and stir aseptically with a sterile glass rod until dispersed. Add additional Lactose Broth to bring the volume to 225 ml., and shake well. Check the pH, and adjust to approximately pH 7. Loosen the cap to permit gas to escape. Incubate at 35° for 24 hours.

Dried Yeast—Weigh 25 g. into a sterile wide-mouth, screw-capped 500-ml. jar. Add 225 ml. of sterile Lactose Broth, and shake vigorously. Loosen the cap to permit gas to escape. Incubate at 35° for 24 hours.

Salmonella Isolation and Presumptive Identification Procedures

Pre-enrichment—From lactose pre-enrichment that has been incubated at least 24 hours, pipet 0.1 ml. into 10 ml. of Selenite-Cystine Broth, and 0.1 ml. into 10 ml. of Tetrathionate Broth. Incubate 24 hours at 35°. (Note—In the testing of thyroid products, use 0.5 ml.; in the testing of dried yeast, use 1.0 ml.)

Enrichment—From Selenite-Cystine Broth and/or Tetrathionate Broth which has been incubated 24 hours at 35°, streak for isolation on the dry surface of XL Agar Modified, Brilliant Green Agar, and Salmonella-Shigella Agar using a needle (or in place of XL Agar Modified, Bismuth Sulfite Agar may be used). The XL Agar should be first streaked, using a needle, then Brilliant Green, then Salmonella-Shigella Agar Modified, and last Bismuth Sulfite Agar, if used. Use a minimum of broth and 3 mm. between each streak mark. Incubate for 24 hours at 35°. Observe for characteristic isolated colonies. Incubate negative plates an additional 24 hours.

Salmonella-Shigella Agar Modified Agar—Salmonella form small, transparent colonies, uncolored or opaque tan colonies, generally smooth, sometimes with black centers.

Brilliant Green Agar—Salmonella form small, smooth, pink, opaque colonies with entire colonies surrounded by a brilliant red zone.

XL Agar Modified—Salmonella form shiny, black colonies, or red colonies with black centers.

Bismuth Sulfite Agar—Salmonella form flat or slightly raised green colonies, or black colonies showing a metallic sheen in sparsely populated areas.

Presumptive Identification—Pick typical colonies, well isolated, from selective agars to Triple Sugar-Iron-Agar slants. Pick from the top of at least two well-isolated colonies, avoiding contact with the agar surface. If colonies are not well-isolated, place a loopful in Selenite-Cystine Broth, incubate 6 to 18 hours, and restreak on selective agars. Surface-streak and stab to the butt of the Triple Sugar-Iron-Agar slant. Incubate at 35° for 24 hours. All slants having alkaline (red) slants and acid (yellow) butts are positive presumptive for Salmonella; hydrogen sulfide is also usually produced, blackening agar due to iron sulfide precipitation.

Confirmation Test—To confirm positive presumptive identification tests, mark a plastic Petri dish into sections about 1 × 2 cm. using a wax pencil. Emulsify a small amount of growth from Triple Sugar-Iron-Agar in 1 drop of 0.85 percent saline in the upper part of a section. Add 1 drop of polyvalent O (somatic) A-I antisera† adjacent to the emulsified culture, and let the 2 drops flow together, or mix with a clean needle.

Tilt to mix for 1 minute, and observe with a hand lens against a dark background, or in a microscope light. Observe agglutinations (clumping) of cells and report as positive or negative.

Cultures not reacting with polyvalent O antisera, or those suspected of being false reactors, should be subjected to additional testing. When such testing is conducted, perform the necessary biochemical and/or serological tests (including use of polyvalent H antisera††) as described in *Enterobacteriaceae, Biochemical Methods for Group Identification*, Public Health Service Publication No. 734 (1962), or in *Identification of Enterobacteriaceae*, P. R. Edwards and W. H. Ewing, Burgess Publishing Co., Minneapolis (1962).

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† Available from Difco Laboratories, Detroit, MI 48201, or from Lederle Laboratories, Pearl River, NY 10965.

†† Available from Baltimore Biological Laboratory (BBL), Division of Bioquest, Cockeysville, MD 21030, or from Difco Laboratories.

SALTS OF ORGANIC NITROGENOUS BASES

Standard Preparation—Unless otherwise directed, prepare a solution in 0.5 *N* sulfuric acid containing, in each ml., about 500 mcg. of the specified Reference Standard, calculated on the dried or anhydrous basis, and accurately weighed.

Assay Preparation—If the dosage form is a tablet, weigh and finely powder not less than 20 tablets, weigh accurately a portion of the powder, equivalent to about 25 mg. of the active ingredient, and transfer it quantitatively to a 125-ml. separator; or, if the dosage form is a liquid, transfer a volume of it, equivalent to about 25 mg. of the active ingredient and accurately measured, to a 125-ml. separator. Then to the separator add 20 ml. of 0.1 *N* sulfuric acid, and shake vigorously for 5 minutes. Add 20 ml. of ether, shake carefully, and filter the acid phase into a second 125-ml. separator. Shake the ether phase with two 10-ml. portions of 0.1 *N* sulfuric acid, filter each portion of acid into the second separator, and discard the ether. To the acid extract add 10 ml. of sodium hydroxide T.S. and 50 ml. of ether, shake carefully, and transfer the aqueous phase to a third 125-ml. separator containing 50 ml. of ether. Shake the third separator carefully, and discard the aqueous phase. Wash the ether extract in the two separators, in succession, with a single 20-ml. portion of water, and discard the water. Extract the separate ether phases successively with 20, 20, and 5 ml. of 0.5 *N* sulfuric acid, combine the acid extracts in a 50-ml. volumetric flask, dilute with the acid to volume, and mix.

Procedure—Unless otherwise directed, dilute 5.0 ml. each of the *Standard Preparation* and the *Assay Preparation* with 0.5 *N* sulfuric acid to 100.0 ml., and concomitantly determine the absorbance of each solution at the specified wavelength, using 0.5 *N* sulfuric acid as the blank. Record the absorbance of the solution from the *Standard Preparation* as A_S and that from the *Assay Preparation* as A_U, and calculate the result of the assay as directed in the individual monograph.

SELENIUM LIMIT TEST

2,3-Diaminonaphthalene Solution—On the day of use, dissolve 100 mg. of 2,3-diaminonaphthalene and 500 mg. of hydroxylamine hydrochloride in sufficient 0.1 *N* hydrochloric acid to make 100 ml.

Selenium Stock Solution—Transfer 120.0 mg. of powdered metallic selenium to a 1000-ml. volumetric flask, and add 100 ml. of dilute nitric acid (1 in 2). Warm gently on a steam bath to effect solution, cool, dilute to volume with water, and mix. Transfer 5.0 ml. of the solution to a 200-ml. volumetric flask, dilute to volume with water, and mix. Each ml. of this solution contains 3 mcg. of selenium.

Standard Selenium Solution—Transfer 2.0 ml. of *Selenium Stock Solution* to a 150-ml. beaker, add 50 ml. of 0.25 *N* nitric acid, and mix.

Test Preparation—Weigh the quantity of sample specified in the individual monograph (and the magnesium oxide, where required), and proceed as directed under *Oxygen Flask Combustion*, page 823, beginning with "Place the sample, together with a filter paper fuse-strip . . . ," using a 1000-ml. combustion flask and 25 ml. of 0.5 *N* nitric acid as the absorbing liquid. (Note: If the sample contains more than 1 percent of moisture, dry it at 140° for 2 hours before combustion.) Following combustion, place a few ml. of water in the cup, loosen the stopper, and rinse the stopper and sample holder, and sides of the flask with about 25 ml. of water. Transfer the solution to a 150-ml. beaker, heat gently to boiling, boil for 10 minutes, and cool.

Procedure—Using dilute ammonium hydroxide (1 in 2), adjust the pH of the

Standard Selenium Solution, the *Test Preparation*, and 50 ml. of 0.25 *N* nitric acid, to serve as the blank, to 2.0 ± 0.2. Add 200 mg. of hydroxylamine hydrochloride to each beaker, swirl gently to dissolve, then without delay add 5 ml. of *2,3-Diaminonaphthalene Solution* to each solution, mix, cover each beaker with a watch glass, and allow to stand for 100 minutes at room temperature. Transfer the solutions to separate separators with the aid of about 10 ml. of water, and extract each solution with 5.0 ml. of cyclohexane, shaking vigorously for 2 minutes. Allow the layers to separate, discard the aqueous phases, transfer the cyclohexane layer from each separator to separate centrifuge tubes, and centrifuge to remove all traces of water. Concomitantly determine the absorbances of the cyclohexane solutions in 1-cm. cells, at the maximum at about 380 mμ, with a suitable spectrophotometer, using the blank to set the instrument. The absorbance of the solution from the *Test Preparation* is not greater than that from the *Standard Selenium Solution* when a 200-mg. sample is used, or is not greater than one-half that from the *Standard Selenium Solution* when a 100-mg. sample is used.

SPECIFIC GRAVITY

Unless otherwise stated in the individual monograph, the specific gravity is based on the ratio of the weight of a substance in air at 25° to the weight of an equal volume of water at the same temperature. When the substance is a solid at 25°, determine the specific gravity at the temperature directed in the respective monograph, and refer to water at 25°.

Procedure—Select a scrupulously clean, dry pycnometer that previously has been calibrated by determining its weight and the weight of recently boiled water contained in it at 25°. Adjust the temperature of the substance to about 20°, and fill the pycnometer with it. Adjust the temperature of the filled pycnometer to 25°, remove any excess of the substance, and weigh. Subtract the tare weight of the pycnometer from the filled weight of the pycnometer.

The specific gravity of the substance is the quotient obtained by dividing the weight of the substance contained in the pycnometer by the weight of water it contained, both determined at 25° unless otherwise directed in the individual monograph.

SPECTROPHOTOMETRY, COLORIMETRY, FLUOROMETRY, NEPHELOMETRY, AND TURBIDIMETRY

Absorption spectrophotometry is the measurement of the absorption, by substances, of electromagnetic radiation of definite and narrow wavelength range, approximating monochromatic radiation.

Atomic absorption spectrophotometry, or absorption flame spectrophotometry, is a measurement procedure during which atoms of an element, upon being atomized into a flame and converted to the ground electronic state, absorb light at a characteristic wavelength which is usually one of the emission spectrum lines for that particular element.

Colorimetry is the commonly accepted term for the measurement of absorption of light, usually in the visible spectrum, which is not monochromatic but is restricted by the use of filters.

Fluorometry is the measurement of the fluorescence, light, or other radiation emitted from a substance while it is being exposed to radiant energy.

Turbidimetry involves measurement of the degree of attenuation of a light beam incident on particles suspended in a medium, the measurement being made in the directly transmitted beam.

Nephelometry involves measurement of the light scattered by suspended particles, the measurement usually being made perpendicularly to the incident beam.

Light scattering involves measurement of the light scattered because of sub-microscopic optical density inhomogeneities of solutions and is useful in the determination of weight-average molecular weights of polydisperse systems in the molecular weight range from a thousand to several hundred million.

The wavelength range available for these measurements extends from the short wavelengths of the ultraviolet through the infrared. For convenience of reference, this spectral range is roughly divided into the ultraviolet (185 mμ to 380 mμ), the visible (380 mμ to 780 mμ), the near-infrared (780 mμ to 3000 mμ), and the infrared (3 μ to 40 μ).

Comparative Utility of Spectral Ranges—For many pharmaceutical substances, measurements can be made in the ultraviolet and visible regions of the spectrum with greater accuracy and sensitivity than in the near-infrared and infrared. When solutions are observed in 1-cm. cells, concentrations of about 10 mcg. of the sample per ml. often will produce absorbances of 0.2 to 0.8. In the infrared and near-infrared, concentrations of 1 to 10 mg. per ml. and up to 100 mg. per ml., respectively, with cell lengths of from 0.01 mm.

to upwards of 3 mm., may be needed to produce sufficient absorption in these ranges.

The ultraviolet and visible spectrum of a substance generally does not have as high a degree of selectivity as the infrared spectrum. Nevertheless, for many substances it is a useful means of identification and quantitative assay.

The near-infrared region is especially suitable for the determination of -OH and -NH groups, such as water in alcohol, -OH in the presence of amines, alcohols in hydrocarbons, and primary and secondary amines in the presence of tertiary amines.

The infrared spectrum is unique for any given chemical compound with the exception of optical isomers, which have identical spectra. However, polymorphism may occasionally be responsible for a difference in the infrared spectrum of a given compound in the solid state. Frequently, small differences in structure result in significant differences in spectra. Because of the large number of maxima in an infrared absorption spectrum, it is sometimes possible to measure quantitatively the individual components of a mixture of known qualitative composition without prior separation.

Fluorometry is often more sensitive than absorption spectrophotometry. In absorption measurements, the sample transmittance is compared to that of a blank; and at low concentrations, both solutions give high signals. Conversely, in fluorometry, the solvent blank has low rather than high output, so that the background radiation ("noise") that may interfere with determinations at low concentrations is much less. Whereas few compounds can be determined conveniently at concentrations below 10^{-5} M by light absorption, it is not unusual to employ concentrations of 10^{-7} to 10^{-8} M in fluorometry.

Theory and Terms—The power of a radiant beam decreases in relation to the distance that it travels through an absorbing medium. It also decreases in relation to the concentration of absorbing molecules, atoms, or ions encountered in that medium. These two factors determine the proportion of the total incident energy that emerges. The decrease in power of monochromatic radiation passing through a homogeneous absorbing medium is stated quantitatively by Beer's law,

$$\log_{10}(1/T) = A = abc,$$

in which the terms are as defined below.

General agreement has not yet been reached on the definitions of spectrophotometric terms. The following definitions and symbols are here designated for National Formulary purposes:

Absorbance [Symbol: A]—The logarithm, to the base 10, of the reciprocal of the transmittance (T). (NOTE: Descriptive terms formerly used include optical density; absorbancy; and extinction.)

Absorptivity [Symbol: a]—The quotient of the absorbance (A) divided by the product of the concentration (c), expressed in g. per liter, of the substance and the absorption path length in cm. (b). (NOTE: This differs from the entity for which the term "absorptivity" was used in NF XI, "specific absorbance" was used in NF X, and "specific absorbancy" was used in NF IX. It is not to be confused with absorbancy index; specific extinction; or extinction coefficient.)

Molar Absorptivity [Symbol: ϵ]—The quotient of the absorbance (A) divided by the product of the concentration, expressed in moles per liter, of the substance (c) and the absorption path length in cm. (b). It is also the product of absorptivity (a) and the molecular weight of the substance. (NOTE: Terms formerly used include molar absorbancy index, molar extinction coefficient, and molar absorption coefficient.)

Absorption Coefficient [Symbol: K_ν]—In atomic absorption spectrophotometry, the absorption coefficient may be defined by its role in the equation,

$$K_\nu d\nu = \pi e^2 N_o f/mc,$$

in which K_ν is the absorption coefficient at frequency ν, e is the electronic charge, m is the electronic mass, c is the velocity of light, N_o is the number of atoms per cubic centimeter capable of absorbing radiation of frequency ν (in the flame a negligible number of atoms are in the excited state), and f is the oscillator strength, which is inversely proportional to the excited state lifetime. The integrated absorption, *i.e.*, the left-hand side of the equation, is directly proportional to N_o since all other right-hand side values are constant.

Absorption Spectrum—A graphic representation of absorbance, or any function of absorbance, plotted against wavelength or function of wavelength.

Transmittance [Symbol: T]—The quotient of the radiant power transmitted by a sample divided by the radiant power incident upon the sample. (NOTE: Terms formerly used include transmittancy; and transmission.)

Turbidance [Symbol: S]—The light-scattering effect of suspended particles. The amount of suspended matter may be measured by observation of either the transmitted light (turbidimetry) or the scattered light (nephelometry). The turbidance is given approximately by the equation,

$$S = \log_{10} P_0/P = \frac{kbcd^3}{d^4 + \alpha\lambda^4},$$

in which S is defined as $\log_{10}(P_0/P)$ and is thus analogous to absorbance; P_0 is the power of the radiation incident upon the sample and P is that of the radiation transmitted; b is the thickness of the sample in the direction of transmission; c is the concentration of suspended matter; d is the average diameter of the particles; λ is the wavelength; k is a proportionality constant that depends on the nature of the suspension and the method of measurement; and α is a constant that depends only on the method. This equation is valid for dilute suspensions, which constitute the only region where the method has analytical utility. In nephelometry, where the scattered radiation is measured generally in a direction normal to the direction of transmission, the mathematics is less convenient. The incident power (P_0) can be assumed to be equal to the sum of the power transmitted (P) and that scattered (P_s). It is easily shown that

$$P_s = P_0 - P = P_0(1 - 10^{-S}).$$

For a given suspension measured with monochromatic radiation in a given apparatus, α, k, b, d, and λ are fixed, so that S is proportional to the concentration c. It is then possible to write,

$$S = Kc, \text{ and } P_s = P_0(1 - 10^{-Kc}),$$

in which K is a new proportionality constant.

Turbidity [Symbol: τ]—In light scattering measurements, the turbidity is defined in terms of attenuation of the radiant power of the incident light beam as is described in the equation

$$I = I_0 e^{-l\tau}$$

in which I is the attenuated beam radiant power, I_0 is the incident beam radiant power, and l is the sample thickness. Since differences in I and I_0 are very small, a convenient means to determine τ is in terms of scattered light at right angles to the incident beam. Thus, for two systems,

$$\frac{R_1}{R_2} = \frac{\tau_1}{\tau_2}$$

in which R_1 and R_2 are the scattering intensities at 90° and τ_1 and τ_2 the respective turbidities.

The phenomenon of light scattering has its origin in the fundamental nature of molecular systems. Although an apparently homogeneous system such as a gas, liquid or solution manifests no change in macroscopic properties at equilibrium, the situation at the sub-microscopic level is different. The thermal energy of gases and liquids is enough to cause local fluctuations in the number of molecules in any typical volume element over intervals of time which are long enough to represent considerable molecular vibrational activity. In solution systems, the average value of these fluctuations is related to osmotic properties and to the turbidity τ and indicates that the solute scattering is much greater than that of the solvent.

When a light beam enters a macroscopically homogeneous system, it is scattered by the scattering elements which result from random variations in optical density at the sub-microscopic level. The role of refractive index is defined by the equation for the refractive index parameter, H,

$$H = \frac{32\pi^3 n_0}{3N\lambda^4}\left(\frac{n - n_0}{c}\right)$$

in which n_0 and n are the refractive indices of the solvent and the solution, respectively, c is the solute concentration in g. per ml. of solution, λ is the wavelength of light, and N is Avogadro's number.

The turbidity, τ, due to the solute may be expressed as

$$\tau = K\left(\frac{G_{90^\circ \text{ soln.}} - G_{90^\circ \text{ solv.}}}{F_1 G_{0^\circ \text{ soln.}} - F_2 G_{0^\circ \text{ solv.}}}\right)$$

in which K is an instrumental constant depending on the geometry of the optics, G is the photocell galvanometer reading, and F is the absorbance of neutral filters.

The relationship of M, the weight-average molecular weight, to the turbidity, τ, and the refractive index parameter, H, is defined by the general 90° light scattering equation

$$\frac{HC}{\tau} = \frac{1}{M} + 2BC$$

in which C is the solute concentration in grams per ml. of solution, and B is a second virial coefficient which is identical with that in the van't Hoff osmotic pressure relationship. Thus, a plot of HC/τ *vs.* C produces a straight line of slope $2B$ and intercept $1/M$. On extrapolation, *i.e.*, $\lim_{c \to 0} HC/\tau$, a value of M may be calculated.

Fluorescence Intensity [Symbol: I] is an empirical expression of fluorescence activity, commonly given in terms of arbitrary units proportional to detector response. The *fluorescence emission spectrum* is a graphical presentation of the spectral distribution of radiation emitted by an activated substance, showing intensity of emitted radiation as ordinate, and wavelength as abscissa. The *fluorescence excitation spectrum* is a graphical presentation of the activation spectrum, showing intensity of radiation emitted by an activated substance as ordinate, and wavelength of the incident (activating) radiation as abscissa. As in absorption spectrophotometry, the important regions of the electromagnetic spectrum encompassed by the fluorescence of organic compounds are the ultraviolet, visible, and near infrared; *i.e.*, the region 250 mμ to

800 mμ. After a molecule has absorbed radiation, the energy can be lost as heat or released in the form of radiation of the same or longer wavelengths as the absorbed radiation. Both absorption and emission of radiation are due to the transitions of electrons between different energy levels, or orbitals, of the molecule. There is a time delay between the absorption and emission of light; this interval, the duration of the excited state, has been measured to be about 10^{-9} to 10^{-8} second for most organic fluorescent solutions. The short lifetime of fluorescence distinguishes this type of luminescence from phosphorescence, which is a long-lived afterglow having a lifetime of 10^{-3} second up to several minutes.

Beer's Law—For most systems used in absorption spectrophotometry, the absorptivity of a substance is a constant independent of the intensity of the incident radiation, the internal cell length, and the concentration, with the result that concentration may be determined photometrically.

Beer's law gives no indication of the effect of temperature, wavelength, or the type of solvent. For most analytical work the effects of normal variation in temperature are negligible.

Deviations from Beer's law may be caused by either chemical or instrumental variables. Apparent failure of Beer's law may result from a concentration change in solute molecules because of association between solute molecules or between solute and solvent molecules, or dissociation or ionization. Other deviations might be caused by polychromatic radiation, slit-width effects, or stray light.

Even at a fixed temperature in a given solvent, the absorptivity may not be truly constant. However, in the case of samples with only one absorbing component, it is not necessary that the absorbing system conform to Beer's law for use in quantitative analysis. The concentration of an unknown may be found by comparison with an experimentally determined standard curve.

Although, in the strictest sense, Beer's law does not hold in atomic absorption spectrophotometry because of the lack of quantitative properties of the cell length and the concentration, the absorption processes taking place in the flame under conditions of reproducible aspiration do follow the Beer relationship in principle. Specifically, the negative log of the transmittance, or the absorbance, is directly proportional to the absorption coefficient, and, consequently, is proportional to the number of absorbing atoms. On this basis, calibration curves may be constructed to permit evaluation of unknown absorption values in terms of concentration of the element in solution.

Use of Reference Standards—With few exceptions, spectrophotometric tests and assays call for comparison against the appropriate NF or USP Reference Standard. The purpose of this is to ensure measurement under conditions identical for the test specimen and the reference substance. These conditions include wavelength setting, slit-width adjustment, cell placement and correction, and transmittance levels. It should be noted that cells exhibiting identical transmittance at a given wavelength may differ considerably in transmittance at other wavelengths. Appropriate cell corrections should be established for use where high precision is required.

The expression, "similarly measured," as it is used in tests and assays involving spectrophotometry, indicates that the reference specimen, generally an NF or USP Reference Standard, is to be prepared and concomitantly measured (see page 9) in a manner identical for all practical purposes to that used for the test specimen. Unless otherwise specified, in making up the solution of the specified Reference Standard, a solution of about the desired concentration (*i.e.*, within 10 percent) should be prepared, and the calculations should be made on the basis of the exact amount weighed out, and, if a previously dried sample of the Reference Standard has not been used, on the dried or anhydrous basis. Unless otherwise directed, Reference Standards should be dried before use as directed in their labeling. If drying instructions are not provided in the labeling, and if drying is not specified in the particular test in the individual monograph, the Reference Standard may be used without drying, in which case the weight of the standard taken should be corrected for *Loss on drying* or *Water*, which are determined as directed in the monograph for the respective drug entity. Special directions may be given in a particular test when the Reference Standard is a hydrate. If it is not feasible to determine the moisture content of the Reference Standard by the titrimetric method, page 900, and if the monograph for the respective drug entity does not contain a test for *Loss on drying*, the Reference Standard should be dried over a suitable desiccant in order to convert the weight of Standard taken to the anhydrous basis, unless otherwise specified.

Apparatus—Many types of spectrophotometers are commercially available. Fundamentally, all types provide for passing essentially monochromatic radiant energy through a sample in suitable form, and measuring the intensity of the fraction that is transmitted. In some instruments the monochromator may be located behind the sample. The spectrophotometer comprises an energy source, a dispersing device with slits for selecting the wavelength band, a cell or holder for the sample, a detector of radiant energy, and associated amplifiers and measuring devices. Some instruments are manually operated, while others are equipped for automatic and continuous recording. Because of the limitation of energy sources, optical materials, and detection devices, no one spectrophotometer generally will function at all wavelengths. Instruments are available for use in the visible; in the visible and ultraviolet; in the visible, ultraviolet, and near-infrared; and in the infrared regions of the spectrum. Choice of the type of spectrophotometric analysis to be used will depend upon a number of factors such as the composition and amount of available sample, the degree of accuracy, sensitivity, and selectivity desired, and the manner in which the sample is handled.

The apparatus used in atomic absorption spectrophotometry has several unique features. For each element to be determined, a specific source which emits the spectral line to be absorbed should be selected. The source is usually a hollow-cathode lamp, the cathode of which is designed to emit the desired radiation when excited. Since the radiation to be absorbed by the sample element is usually of the same wavelength as that of its emission line, the element in the hollow-cathode lamp will be the same as the element to be determined. The apparatus is equipped with an aspirator for introducing the sample into a flame, which is usually provided by air-acetylene, air-hydrogen, or, for refractory cases, nitrous oxide-acetylene. The flame, in effect, is a heated sample chamber. A detector is used to read the signal from the chamber. Interfering radiation produced by the flame during combustion may be negated by the use of a chopped source lamp signal of a definite frequency. The detector should be tuned to this alternating current frequency so that the direct current signal arising from the flame will be ignored. The detecting system, therefore, reads only the change in signal from the hollow-cathode source, which is directly proportional to the number of atoms to be determined in the sample. For National Formulary purposes, apparatus which provides the readings directly in absorbance units is usually required. However, instruments providing readings in percent transmission, percent absorption, or concentration may be used if the calculation formulas provided in the individual monographs are revised as necessary to yield the required quantitative results. Percent absorption or percent transmittance may be converted to absorbance, A, by the following two equations: $A = 2 - \log_{10} (100 - \%\text{ absorption})$; or $A = 2 - \log_{10} \%$ transmittance. Depending upon the type of apparatus used, the readout device may be a meter, digital counter, recorder, or printer. Both single-beam and double-beam instruments are commercially available, and either is suitable.

Light scattering instruments are available and consist in general of a mercury lamp, with filters for the strong green or blue lines, a shutter, a set of neutral filters with known transmittance and a sensitive photomultiplier to be mounted on an arm which can be rotated around the solution cell and set at any angle from −135° to 0° to +135° by a dial outside the light-tight housing. Solution cells are of various shapes such as square for measuring 90° scattering, semioctagonal for 45°, 90° and 135° scattering and cylindrical for scattering at all angles. Since the determination of molecular weight requires a precise measure of the difference in refractive index between the solution and solvent, $\left(\frac{n - n_0}{c}\right)$ a second instrument, a differential refractometer, is needed to measure this small difference.

Measurement of fluorescence intensity can be made with a simple *filter fluorometer.* Such an instrument consists of a radiation source, a primary filter, a sample chamber, a secondary filter, and a fluorescence detection system. In most such fluorometers, the detector is placed on an axis at 90° from that of the exciting beam. This right-angle geometry permits the exciting radiation to pass through the sample and not contaminate the output signal received by the fluorescence detector. However, the detector unavoidably receives some of the exciting radiation as a result of the inherent scattering properties of the solutions themselves, or if dust or other solids are present. Filters are used to eliminate this residual scatter. The primary filter selects short wavelength radiation capable of exciting the sample, while the secondary filter is normally a sharp cut-off filter that allows the longer wavelength fluorescence to be transmitted but blocks the scattered excitation.

Most fluorometers use photomultiplier tubes as detectors, many types of which are available, each having special characteristics with respect to spectral region of maximum sensitivity, gain, and electrical noise. The photocurrent is amplified and read out on a meter or recorded.

A *spectrofluorometer* differs from a filter fluorometer in that filters are replaced by monochromators, of either the prism or the grating type. For analytical purposes, the spectrofluorometer is superior to the filter fluorometer in wavelength selectivity, flexibility, and convenience, in the same way in which a spectrophotometer is superior to a filter photometer.

Many radiation sources are available. Mercury lamps are relatively stable and emit energy mainly at discrete wavelengths. Tungsten lamps provide an energy continuum in the visible region. The high pressure xenon arc lamp is often used in spectrofluorometers because it has an energy continuum extending from the ultraviolet into the infrared.

In spectrofluorometers, the monochromators are equipped with slits. A narrow slit provides high resolution and spectral purity, while a large slit sacrifices these for high sensitivity. Choice of slit size is determined by the separation between exciting and emitting wavelengths as well as the degree of sensitivity needed.

Sample cells used in fluorescence measurements may be round tubes or rectangular cells similar to those used in absorption spectrophotometry, except that they are polished on all four vertical sides. A convenient sample size is 2 to 3 ml., but some instruments can be fitted with small cells holding 0.1 to 0.3 ml., or with a capillary holder requiring even less sample.

Procedure

Spectrophotometry—Detailed instructions for operating spectrophotometers are supplied by the manufacturers. To achieve significant and valid results, the operator of a spectrophotometer should be aware of its limitations and of potential sources of error and variation. The instruction manual should be followed closely on such matters as care, cleaning, and calibration of the instrument, and techniques of handling absorption cells, as well as instructions for operation. In atomic absorption spectrophotometry, the techniques of handling the burner-aspirator should receive particular attention. The following points require special emphasis.

Check the instrument for accuracy of calibration. Where a continuous source of radiant energy is used, attention should be paid to both the wavelength and photometric scales; where a spectral line source is used, only the photometric scale need be checked. A number of sources of radiant energy have spectral lines of suitable intensity, adequately spaced throughout the spectral range selected. The best single source of ultraviolet and visible calibration spectra is the quartz-mercury arc, of which the lines at 253.7, 302.25, 313.16, 334.15, 365.48, 404.66, and 435.83 mμ may be used. The glass-mercury arc is equally useful above 300 mμ. The 486.13-mμ and 656.28-mμ lines of a hydrogen discharge lamp may be used also. The wavelength scale may be calibrated also by means of suitable glass filters, which have useful absorption bands through the visible and ultraviolet regions. Standard glasses containing didymium (a mixture of praseodymium and neodymium) have been used widely. Glass containing holmium* is considered superior. The wavelength scales of near-infrared and infrared spectrophotometers are readily checked by the use of absorption bands provided by polystyrene films, carbon dioxide, water vapor, or ammonia gas.

For checking the photometric scale, a number of standard inorganic glass filters as well as standard solutions of known transmittances such as potassium chromate or potassium dichromate are available.†

Comparisons of a sample with a reference standard are best made at a peak of spectral absorption for the compound concerned. Assays prescribing spectrophotometry give the commonly accepted wavelength for peak spectral absorption of the substance in question. It is known that different spectrophotometers may show minor variation in the apparent wavelength of this peak. Good practice demands that use be made of the peak wavelength actually found in the individual instrument, rather than the specific wavelength given in the monograph, provided the two do not differ by more than ±2 mμ. If the difference is greater, recalibration of the instrument may be indicated.

Sample Preparation—For determinations utilizing ultraviolet or visible spectrophotometry, the specimen generally is dissolved in a solvent. Many solvents are suitable for these ranges, including water, alcohols, chloroform, lower hydrocarbons, ethers, and dilute solutions of ammonium hydroxide, sodium hydroxide, sulfuric acid, or hydrochloric acid. Precautions should be taken to utilize solvents free from contaminants absorbing in the spectral region being used. It is usually advisable to use water-free methanol or alcohol, or alcohol denaturated by the addition of methanol but not containing benzene or other interfering impurities. Solvents of special spectrophotometric quality, guaranteed to be free from contaminants, are available commercially from several sources.

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* Certified holmium glass filters are obtainable from the National Bureau of Standards (202, 165g, and 165h). The same type of filter, without certification, is obtainable from Corning Glass Co., Corning, N. Y. (Cat. No. 3130). The performance of an uncertified filter should be checked against one which has been properly certified.

† For further detail regarding checks on both the wavelength and the photometric scales of a spectrophotometer, reference may be made to the following publications of the National Bureau of Standards, Department of Commerce, Washington, DC 20204: "Standards for Checking the Calibration of Spectrophotometers (200 to 1000 mμ)," Letter Circular LC-1017, January, 1955; "Spectrophotometry (200 to 1000 mμ)," Circular 484, September 15, 1949; "Calibrating Wave Lengths in the Region from 0.6 to 2.6 μ," *J. Research N.B.S.*, **49**, 13 (1952), RP 2338, and "Reference Wave Lengths for Calibrating Prism Spectrometers," *J. Research, N.B.S.* **58,** 195 (1957), RP 2752.

No solvent in appreciable thickness is completely transparent through the near-infrared and infrared spectrum. Carbon tetrachloride is practically transparent (up to 5 mm. in thickness) to 6 μ. Carbon disulfide (1 mm. in thickness) is suitable as a solvent to 40 μ with the exception of the 4.2-μ to 5.0-μ and the 5.5-μ to 7.5-μ regions, where it has strong absorption. Other solvents have relatively narrow regions of transparency. For infrared spectrophotometry, an additional qualification for a suitable solvent is that it must not affect the material, usually sodium chloride, of which the cell is made. Other methods for sample preparation include dispersing the finely ground solid specimen in mineral oil, or incorporating it in a transparent disk or pellet obtained by mixing it intimately with previously dried potassium bromide and pressing the mixture in a die. While the infrared region of the spectrum extends from about 3 μ to 40 μ, comparative spectra, obtained to ascertain compliance with a monograph specification for *Infrared absorption*, are generally determined in the range from 3 μ to 15 μ unless otherwise specified.

When values for infrared line spectra are given in an individual monograph, the letters *s*, *m*, and *w* signify strong, medium, and weak absorption, respectively; *sh* signifies a shoulder, *bd* signifies a band, and *v* = very. The values may vary as much as 0.1 μ, depending upon the particular instrument used.

Polymorphism gives rise occasionally to variations in the infrared spectra of some compounds in the solid state. Therefore, when conducting *Infrared absorption* tests, or identification tests, if a difference appears in the infrared spectra of the sample and the standard, dissolve portions of both the sample and the standard in a suitable solvent, evaporate the solutions to dryness, and repeat the test on the residues.

In atomic absorption spectrophotometry, the nature of the solvent and the concentration of solids must be given special consideration. An ideal solvent is one that interferes to a minimal extent in the absorption or emission processes and one that produces neutral atoms in the flame. If there is a significant difference between the surface tension or viscosity of the sample and standard solutions, the solutions will be aspirated or atomized at a different rate, causing significant differences in the signals generated. The acid concentration of the solutions also affects the absorption processes. Thus, the solvent used in preparing the sample and the standard should be the same or as much alike in these respects as possible, and should yield solutions that are easily aspirated *via* the sample tube of the burner-aspirator. Since solids present in the solutions may give rise to matrix or bulk interferences, the total solids content in all solutions should be kept below 2 percent wherever possible.

Colorimetry—Colorimetric assays usually call for comparing concomitantly the absorbance produced by the *Assay preparation* with that produced by a *Standard preparation* containing approximately an equal quantity of a reference standard. In some situations, it is permissible to omit the use of a reference standard. This is true when colorimetric assays are made with routine frequency, and when a suitable standard curve is available, prepared with the respective NF or USP Reference Standard, and when the substance assayed conforms to Beer's law within the range of about 75 percent to 125 percent of the final concentration used in the assay. Under these circumstances, the absorbance found in the assay may be interpolated on the standard curve, and the assay result calculated therefrom.

Such standard curves should be confirmed frequently, and always when a new colorimeter or new lots of reagents are put into use.

In colorimetric assays that direct the preparation and use of a standard curve, it is permissible and preferable, when the assay is employed infrequently, not to use the standard curve but to make the comparison directly against a quantity of the Reference Standard approximately equal to that taken of the sample, and similarly treated.

Visual Comparison—Where a color or a turbidity comparison is directed, color-comparison tubes that are matched as closely as possible in internal diameter and in all other respects should be used. For color comparison, the tubes should be viewed downward, against a white background, with the aid of a light source directed from beneath the bottoms of the tubes, while for turbidity comparison the tubes should be viewed horizontally, against a dark background, with the aid of a light source directed from the sides of the tubes.

In conducting limit tests that involve a comparison of colors in two like containers (*e.g.*, matched color-comparison tubes), a suitable instrument, rather than the unaided eye, may be used.

Fluorometry—The measurement of fluorescence is a useful analytical technique. *Fluorescence* is light emitted from a substance in an excited state that has been reached by the absorption of radiant energy. A substance is said to be *fluorescent* if it can be made to fluoresce. Many compounds can be assayed by procedures utilizing either their inherent or their derived fluorescence.

Samples prepared for fluorometry are usually one-tenth to one-hundredth as concentrated as those used in absorption spectrophotometry, for the following reason. In analytical applications, it is preferable that the fluorescence signal be linearly related to the concentration; but if a sample is too concentrated, a significant part of the incoming light is absorbed by the sample near the cell surface, thus resulting in a reduction of the light reaching the center. That is, the sample itself acts as an "inner filter." Fortunately, fluorometry is inherently a very sensitive technique, and concentrations of 10^{-5} to 10^{-7} M frequently are used. It is necessary in any analytical procedure to make a working curve of fluorescence intensity-versus-concentration in order to establish a linear relation. All readings should be corrected for a solvent blank.

Fluorescence measurements are sensitive to the presence of dust and other solid particles in the sample. Such impurities may reduce the intensity of the exciting beam or give misleading high readings because of multiple reflections in the sample cell. It is therefore wise to eliminate solid particles by centrifugation; filtration also may be used, but some filter papers contain fluorescent impurities.

Temperature regulation is often important in fluorometry. For some substances, fluorescence efficiency may be reduced by as much as 1 to 2 percent per degree of temperature rise. In such cases, if maximum precision is desired, temperature-controlled sample cells are useful. For routine analysis, it may be sufficient to make measurements rapidly enough so that the sample does not heat up appreciably from exposure to the intense light source. Many fluorescent compounds are light-sensitive. Exposed in a fluorometer, they may be photo-degraded into more or less fluorescent products. Such effects may be detected by observing the detector response in relation to time, and may be reduced by attenuating the light source with filters or screens.

Change of solvent may markedly affect the intensity and spectral distribution of fluorescence. It is inadvisable, therefore, to alter the solvent specified in established methods without careful preliminary investigation. Many compounds are fluorescent in organic solvents but virtually nonfluorescent in water; thus, a number of solvents should be tried before it is decided whether or not a compound is fluorescent. In many organic solvents, the intensity of fluorescence is increased by elimination of dissolved oxygen, which has a strong quenching effect. Oxygen may be removed by bubbling an inert gas such as nitrogen or helium through the sample.

A semiquantitative measure of the strength of fluorescence is given by the ratio of the fluorescence intensity of a sample and that of a standard obtained with the same instrumental settings. Frequently, a solution of stated concentration of quinine in 0.1 N sulfuric acid or fluorescein in 0.1 N sodium hydroxide is used as a reference standard.

Turbidimetry and Nephelometry—Turbidity can be measured with a standard photoelectric filter photometer or spectrophotometer, preferably with illumination in the blue portion of the spectrum. Nephelometric measurements require an instrument with a photocell placed so as to receive scattered rather than transmitted light; this geometry applies also to fluorometers, so that, in general, fluorometers can be used as nephelometers, by proper selection of filters.

In practice, it is advisable to ensure that settling of the particles being measured will be negligible. This is usually accomplished by including a protective colloid in the liquid suspending medium. It is important that results be interpreted by comparison of readings with those representing known concentrations of suspended matter, produced under exactly the same conditions.

Turbidimetry or nephelometry may be useful for the measurement of precipitates formed by the interaction of very dilute solutions of reagents, or other particulate matter, such as suspensions of bacterial cells. In order that consistent results may be achieved, all variables must be carefully controlled. Where such control is possible, extremely dilute suspensions may be measured.

Light Scattering—The sample solute is dissolved in the solvent at several different accurately known concentrations, the choice of concentrations being dependent on the molecular weight of the solute and ranges from 1% for $M_w = 10{,}000$ to 0.01% for $M_w = 1{,}000{,}000$. Each solution must be very carefully cleaned before measurement by repeated filtration through fine filters. A dust particle in the solution vitiates the intensity of the scattered light measured. A criterion for a clear solution is when the dissymmetry, 45°/135° scattered intensity ratio, has attained a minimum.

The turbidity and refractive index of the solutions are measured. From the general 90° light scattering equation, a plot of $HC/vs.\ C$ is made and extrapolated to infinite dilution and the weight-average molecular weight, M, is calculated from the intercept, $1/M$.

STERILITY TESTS*

Sterility tests are highly exacting and should be conducted by personnel having had expert training and experience in rigid aseptic techniques. Testing should not be conducted under direct exposure to ultraviolet light or in areas under aerosol treatment. Suitable environmental control tests, including plate counts, should be performed at regular intervals.

Media

Test media may be prepared as described below, or dehydrated mixtures may be used provided that, when reconstituted as directed by the manufacturer or distributor, they have the same ingredients as, and yield media comparable to, those obtained from the formulas given herein.

Test each lot of medium for sterility and for its growth-promoting qualities, using two or more strains of microorganisms that are exacting in their nutritive requirements. Confirm the sterility by incubating samples of the Thioglycollate Media for 24 hours and of the Fluid Sabouraud Medium for 4 days at the temperatures specified herein for their use, and further by using representative uninoculated tubes for the required incubation period during each test.

For sterility tests, place the media in glass containers, preferably of the dimensions given for the required volumes of medium listed: 15 ml., 20 × 150 mm.; 40 ml., 25 × 200 mm.; and 75 to 100 ml., 38 × 200 mm. If larger volumes of medium are required, glass containers providing a similar ratio of surface area to depth of medium should be used, except in the case of Fluid Sabouraud Medium for which a larger surface area is desirable. For the Alternative Thioglycollate Medium, Smith or Durham fermentation tubes are to be used.

Thioglycollate Media must have growth-promoting, buffering and oxygen-tension controlling properties equal to, or better than, those of the media prepared from the following formulas.

I. Fluid Thioglycollate Medium

L-Cystine	500 mg.
Agar, granulated (moisture content not in excess of 15 per cent)	750 mg.
Sodium Chloride	2.5 g.
Dextrose	5.5 g.
Yeast Extract (water-soluble)	5.0 g.
Pancreatic Digest of Casein	15.0 g.
Sodium Thioglycollate	500 mg.
or Thioglycollic Acid	0.3 ml.
Resazurin Sodium Solution (1 in 1000), freshly prepared	1.0 ml.
Water	1000 ml.

Mix the L-cystine, agar, sodium chloride, dextrose, water-soluble yeast extract, and pancreatic digest of casein with 1000 ml. of water, and heat on a steam bath until solution is effected. Dissolve the sodium thioglycollate or thioglycollic acid in the solution and, if necessary, adjust the solution with 1 *N* sodium hydroxide so that, after sterilization, it will have a pH of 7.1 ± 0.1. If filtration is necessary, heat the solution again without boiling, and filter while hot through moistened filter paper. Add the resazurin sodium solution, mix, place the medium in suitable culture tubes, and sterilize in an autoclave at 121° for 20 minutes. The autoclave temperature should be reached within 10 minutes. Cool at once to 25°, and store the medium preferably between 20° and 30°, protected from light. Do not use this medium if evaporated to an extent affecting its fluidity. If more than the upper one-third has acquired a pink color, the medium may be restored once by heating on a steam bath or in free-flowing steam until the pink color disappears.

II. Alternative Thioglycollate Medium

Fluid Thioglycollate Medium is unsuitable for turbid products and for products in which its viscosity interferes with the conduct of the test. Alternative Thioglycollate Medium is acceptable in place of Fluid Thioglycollate Medium for the testing of such products, provided it is freshly prepared or is boiled and cooled just prior to use.

L-Cystine	500 mg.
Sodium Chloride	2.5 g.
Dextrose	5.5 g.
Yeast Extract (water-soluble)	5.0 g.
Pancreatic Digest of Casein	15.0 g.
Sodium Thioglycollate	500 mg.
or Thioglycollic Acid	0.3 ml.
Water	1000 ml.

Heat the ingredients in a suitable container on a steam bath until solution is effected. Mix, and, if necessary, adjust the solution with 1 *N* sodium hydroxide so that, after sterilization, it will have a pH of 7.1 ± 0.1. Filter, if necessary, place in fermentation tubes, and sterilize in an autoclave at 121° for 20 minutes. The autoclave temperature should be reached within 10 minutes.

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* Note—All temperatures herein specified are in centigrade (Celsius) degrees and, with respect to autoclaves, generally mean the exhaust line temperatures.

III. Fluid Sabouraud Medium

Dextrose	20 g.
Pancreatic Digest of Casein	5 g.
Peptic Digest of Animal Tissue	5 g.
Water, to make	1000 ml.

Dissolve the dextrose, the pancreatic digest of casein, and the peptic digest of animal tissue in the water with the aid of gentle heat. Adjust the medium with 1 *N* sodium hydroxide so that, after sterilization, it will have a pH of 5.7 ± 0.1. Filter if necessary, place in culture tubes, and sterilize at 121° for 20 minutes. The autoclave temperature should be reached within 10 minutes.

Procedure

Transfer specified amounts of the product under test to suitable amounts of medium. After appropriate incubation, examine for the presence of viable microorganisms.

If on the first test no growth is found, the material under examination meets the requirements for *Sterility*. If growth is found, the test may be repeated to rule out laboratory contamination which may be introduced during the test, using twice the number of samples. Observe special precautions to ensure that the sample for the re-test is representative of the sterilizer load or filling operation.

Specific procedures for repeat tests must be devised and the results interpreted by the responsible head of the testing laboratory, since they will vary with the product, the sterilization process applied, the types of organisms encountered, and other factors. If repeat tests confirm the presence of contamination, the material under examination fails to meet the requirements for *Sterility*.

The nature of the product determines the selection of the specific sterility test from those procedures set forth in the following sections. The interpretation of all results, regardless of the type of product, is as covered in the foregoing paragraphs.

Bacteriostasis and Fungistasis—In order to avoid false negative results, establish the level of bacteriostatic activity for each product by the following procedure.

To each of several tubes containing the specified amount (15, 40, or 100 ml.) of Fluid Thioglycollate Medium add the specified amount of the product. Inoculate these tubes of product-medium mixtures and the control tubes of medium only, with dilute cultures of bacteria known to be sensitive to the product being tested, including spores of aerobic and anaerobic bacilli. Incubate all tubes at 30° to 32° for at least 7 days.

In a similar manner, determine the fungistatic activity of the product in Fluid Sabouraud Medium, using a 1 in 1000 dilution of a 24- to 28-hour culture of *Candida albicans* in Fluid Sabouraud Medium as a test culture. Incubate at 22° to 25° for at least 10 days.

If growth of the test organisms comparable to that in the control tubes occurs in the product-medium mixtures, use the amounts of product and medium regularly specified.

If the product is bacteriostatic or fungistatic when tested as described above, a suitable sterile inactivating agent, if available, must be used. If an inactivating agent is not available, establish, as described below, suitable amounts of product and medium to be used.

Repeat the above tests using the specified amount of product and larger volumes of the medium to determine the ratio of product to medium in which growth of the test organisms is not affected.

If the specified amount of product is bacteriostatic or fungistatic in 100 ml. of the medium, decrease the amount of the product to find the maximum amount which does not materially affect the growth of the test organisms in 100 ml. of the medium. For liquids and suspensions, if this amount is less than 1 ml., increase the quantity of medium so that the 1 ml. is sufficiently diluted to prevent inhibition of growth. For solids which are not readily soluble or dispersible, if the amount is less than 50 mg., increase the quantity of medium so that the 50 mg. is sufficiently diluted to prevent inhibition of growth. In either case, use the amounts of product and medium established in this manner for routine testing.

Liquids and Suspensions

Sampling—For products which are sterilized with steam under pressure in the final sealed containers, select 10 or more units from each sterilizer load for the test. It is imperative that these samples be representative of all layers of the load.

For all other products, select for the test a total of 20 or more units representative of each batch. In the case of aseptically-filled products, select the units at regular intervals throughout each filling operation. The term "filling operation" refers to any period during which there is no change in the filling assembly or equipment, and which is no longer than one working day or shift.

Opening Containers—Cleanse the exterior surfaces of ampuls and closures of vials with a suitable bactericidal agent. Open ampuls with a sterilized file. If the vial contents are packaged under vacuum, admit sterile air by means of suitable sterile equipment, such as a sterile needle attached to a syringe barrel filled with sterile nonabsorbent cotton.

Culturing—Remove liquids or suspensions for culturing with a sterile pipet or with a sterile syringe and needle. When testing final containers of a product, plant a portion of the material from each container into a tube of Fluid Thioglycollate Medium. In addition, when the final container has not been heated to a least 100° for as long as 15 minutes, plant a portion from each container into a tube of Fluid Sabouraud Medium. Where the volume of product in the containers selected is insufficient for seeding both the Fluid Thioglycollate and Fluid Sabouraud Media, use separate containers for inoculating the two media. Use not less than the volumes of the product and of the medium indicated in the accompanying table.

Container Content, ml.	Minimum Volume of Product, ml.	Minimum Volume of Medium, ml.
10 or less	1, or total content if less than 1 ml.	15
From 10 to 50	5	40
More than 50	10	40

Mix the liquid thoroughly with the medium. If the test material is an oil, shake the mixture thoroughly at the time of planting and at frequent intervals thereafter during the incubation period. Incubate the tubes of Fluid Thioglycollate Medium at 30° to 32° for not less than 7 days, and the Fluid Sabouraud Medium at 22° to 25° for not less than 10 days.

When the material to be tested renders the medium turbid so that the presence or absence of growth cannot be determined readily by visual examination, transfer suitable portions of this turbid medium to fresh medium between the third and seventh days after the test is started. Incubate both the original and transfer tubes for 7 to 11 days. Examine all tubes during and at the end of the incubation period.

Where evidence of growth is observed within 2 days, check the tubes showing such evidence by microscopic examination of stained smears or by transfer to a suitable medium.

Crystalline or Powdered Solids

Sampling—Proceed as directed under *Liquids and Suspensions.*

Opening Containers—Proceed as directed under *Liquids and Suspensions.*

Culturing—Transfer an amount of the product in the form of a dry solid (or of a solution or a suspension of the product prepared by adding sterile diluent to the immediate container), corresponding to 300 mg. from each container being tested, or the entire contents if less than 300 mg., to not less than 40 ml. of Fluid Thioglycollate Medium and to not less than 40 ml. of Fluid Sabouraud Medium, respectively. Mix thoroughly. Proceed as directed for *Culturing* under *Liquids and Suspensions,* beginning with "Incubate the tubes . . . ."

STEROID ASSAY

This assay is generally useful for corticosteroids but is intended for use only in those monographs which make specific reference to it.

Standard Preparation—Dissolve, in alcohol, a suitable quantity of the NF Reference Standard designated in the individual monograph, previously dried at 105° for 3 hours and accurately weighed, and prepare by stepwise dilution, a solution in alcohol containing about 10 mcg. per ml. Pipet 20.0 ml. of this solution into a glass-stoppered, 50-ml. conical flask.

Assay Preparation—Prepare as directed in the individual monograph.

Procedure—To each of the flasks containing the *Assay Preparation* and the *Standard Preparation,* and a similar flask containing 20.0 ml. of alcohol, to serve as the blank, add 2.0 ml. of blue tetrazolium T.S., mix, then to each flask add 2.0 ml. of dilute (1 in 10 with alcohol) tetramethylammonium hydroxide T.S. Mix, allow to stand in the dark for 90 minutes, or the time specified in the individual monograph, and concomitantly determine the absorbances of the solutions obtained from the *Assay Preparation* and the *Standard Preparation,* respectively, at 525 mμ with a suitable spectrophotometer, using the blank to set the instrument. Designate the absorbance of the solution from the *Standard Preparation* as A_S, and that from the *Assay Preparation* as A_U. Calculate the results by the formula given in the individual monograph in which C is the concentration, in mcg. per ml., of the Reference Standard in the *Standard Preparation.*

STEROID CHROMATOGRAPHIC PURITY

Standard Preparation—Dissolve in a mixture of equal volumes of alcohol and chloroform a suitable quantity of the Reference Standard specified in the individual monograph, previously dried at 105° for 3 hours and accurately weighed, to obtain a solution having a concentration of about 8 mg. per ml.

Test Preparation—Prepare as directed in the individual monograph.

Procedure—Coat a 20 × 20-cm. chromatographic plate with a 0.25-mm. layer of chromatographic silica gel mixture, dry for 15 minutes at room temperature, heat at 105° for 1 hour, and cool in a desiccator. Divide the area of the plate into three equal sections, the left and right sections to be used for the *Test Preparation* and the *Standard Preparation*, respectively, and the center section for the blank. Apply 50 µl. each of the *Test Preparation* and of the *Standard Preparation* as streaks 2.5 cm. from the bottom of the designated section of the plate, and dry the streaks with a stream of air. Using the solvent system specified in the individual monograph, develop the chromatogram in a suitable chromatographic chamber (see page 791), previously equilibrated and lined with absorbent paper, until the solvent front has moved about three-fourths of the length of the plate. Remove the plate, evaporate the solvent, and locate the principal band occupied by the *Standard Preparation* by viewing under shortwave ultraviolet light. Mark this band and the corresponding bands in the sections of the plate representing the *Test Preparation* and the blank, respectively. Quantitatively remove the silica gel containing these bands, and transfer to separate glass-stoppered, 50-ml. centrifuge tubes. Add 25.0 ml. of dehydrated alcohol to each tube, shake for 2 minutes, and centrifuge for 5 minutes at about 1500 r.p.m. Concomitantly determine the absorbances of the solutions in 1-cm. cells, at the wavelength specified in the individual monograph, with a suitable spectrophotometer, using the blank to set the instrument. Record the absorbance of the solution from the *Standard Preparation* as A_S and that from the *Test Preparation* as A_U.

SULFONAMIDES

Determination of Individual Sulfonamides in Mixed Sulfonamides

Standard Preparation—An individual *Standard Preparation* is required for each sulfonamide being determined. Transfer about 50 mg., accurately weighed, of the pertinent NF or USP Reference Standard to a 50-ml. volumetric flask containing 1.5 ml. of stronger ammonia water, add methanol, dissolve, dilute to volume with methanol, and mix. Transfer 1.0 ml. of this solution to a 100-ml. volumetric flask, dilute to volume with 0.12 *N* hydrochloric acid, and mix. (Note—The methanol solutions are stable for at least a week, and the acid solutions for at least a month.)

Mixed Standard Preparation—Transfer 1.0 ml. of each required *Standard Preparation* to a small glass-stoppered flask, and mix. (Note—This standard is used to identify the components of the *Assay Preparation* on the chromatogram.)

Assay Preparation—Prepare as directed in the individual monograph.

Procedure—Prepare the necessary number of chromatographic sheets (Whatman No. 1 filter paper or equivalent) about 20 × 20 cm. in size, by drawing a pencil line parallel to and 2.5 cm. from one edge of the paper. Mark the line at points 2.5 cm. and 5 cm from each edge of the paper. Impregnate the paper by dipping it in the immobile solvent (prepared fresh by dissolving 30 ml. of redistilled formamide in 70 ml. of acetone) for 30 seconds. Remove the paper, drain for 10 seconds, and blot between filter paper. Place the impregnated paper on dry filter paper, and air dry for 3 to 5 minutes. With a micropipet, and with repeated applications, streak 100 µl. of the *Assay Preparation* along the starting line, applying the volume in 5 streaks of about 20-µl. each and evaporating the solvent with a gentle current of air between applications. (Note—Make the streak as narrow as possible along the starting line, and keep within the 5-cm. border.) Rinse the tip of the pipet with a drop of methanol-ammonia T.S. mixture (9:1), and then streak the rinse along the starting line between the 5-cm. and 2.5-cm. points at the right edge. Repeat the rinsing with two additional drops, and then blow out the pipet.

Spot 10 µl. of the *Mixed Standard Preparation* at the mark 2.5 cm. from the left edge.

Place 50 ml. of methylene chloride (mobile solvent) in a tray in a 23 × 23 × 7.5-cm. chromatographic chamber arranged for ascending chromatography (see page 789), and allow the chamber to equilibrate about 15 minutes. Remove the cover, place from 7 to 10 ml. of water in a second tray, and without delay, suspend the prepared chromatographic paper sheet so that it dips into the mobile solvent. Cover and seal the chamber, and allow the chromatogram to develop for 1 hour. Remove the paper from the chamber, and allow to air dry for 5 minutes. Place the chromatogram on a dry sheet of filter paper, and view it under shortwave ultraviolet light. (Note—Conduct the following identification and marking without delay to avoid excessive exposure of the sulfonamide spots to ultraviolet irradiation.) Identify and mark the respective spots by matching R_f values with those of the spots produced by the *Mixed Chromatographic Standard.* (Note—Sulfadiazine and sulfamerazine are chromatographed with increasing R_f, respectively.)

Cut the marked zones from the paper, cut each zone into 5 or 6 pieces, and place the pieces from each spot in separate 50-ml. glass-stoppered flasks. Add 20.0 ml. of 0.12 *N* hydrochloric acid to each flask, and allow to stand for about 30 minutes, swirling each flask at least 5 times during this period. Filter the solutions through dry glass wool into separate test tubes, discarding the first 5 ml. of filtrate. Transfer 5.0 ml. of the subsequent filtrate from each solution into separate 10-ml. volumetric flasks. Transfer 3.0 ml. of each required *Standard Preparation* into separate 10-ml. volumetric flasks. To each flask, and to a blank flask containing 5 ml. of 0.12 *N* hydrochloric acid, add 1.0 ml. of sodium nitrite solution and 0.1 ml. of hydrochloric acid, and allow to stand for 5 minutes with frequent swirling. To each flask add 1.0 ml. of ammonium sulfamate solution (1 in 200), and allow to stand for 5 minutes, swirling frequently. Finally, to each flask add 1.0 ml. of freshly prepared *N*-(1-naphthyl)ethylenediamine dihydrochloride solution (1 in 1000), mix, dilute to volume with water, and mix. Allow each solution to stand not less than 15 minutes nor more than 60 minutes, and then concomitantly determine the absorbance of each solution, in 1-cm. cells, recording the spectra from 440 mμ to 700 mμ, with a suitable spectrophotometer, using the blank to set the instrument. Draw a baseline, and determine the corrected absorbance for each solution at the maximum at about 545 mμ.

Calculate the concentration, in mg. per ml., of each sulfonamide in the *Assay Preparation* by the formula $0.12C \times A_U/A_S$, in which C is the exact concentration, in mcg. per ml., of the pertinent *Standard Preparation*, A_U is the corrected absorbance of the *Assay Preparation*, and A_S is the corrected absorbance of the pertinent *Standard Preparation.* From the concentration of the *Assay Preparation* thus determined and applying appropriate dilution factors, calculate the percent of sulfonamide in the sample taken.

TABLET DISINTEGRATION TEST

This test is provided to determine compliance with the limits on *Disintegration* stated in the individual monographs except where the tablets concerned exceed 15 mm. in diameter or are intended for hypodermic solutions, use as troches, or to be chewed, or are designed to liberate the drug content gradually over a period of time or to release the drug over two or more separate periods with a distinct time interval between such release periods. Determine the type of tablets under test from the labeling. Select 6 or more tablets, and subject them to the appropriate procedure described herein.

For the purposes of this test, disintegration does not imply complete solution of the tablet or even of its active constituent. Complete disintegration is defined as that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen is a soft mass having no palpably firm core.

The time stated in the individual monograph is a limit marking the period during which all of the tablets disintegrate, or the proportion of the total number of tablets indicated in the appropriate subsection of this chapter disintegrate.

Apparatus—The apparatus* consists of a basket rack assembly, a suitable vessel for the immersion fluid (preferably a 1-liter beaker), a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 28 and 32 cycles per minute through a distance of not less than 5 cm. and not more than 6 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm. below the surface of the water and descends to not less than 2.5 cm. from the bottom of the vessel on the downward stroke.

Basket-rack Assembly—The basket-rack assembly consists of 6 open-end glass tubes, each 7.75 ± 0.25 cm. long and having an inside diameter of approximately 21.5 mm. and a wall approximately 2 mm. thick; the tubes are held in a vertical position by two plastic plates, each about 9 cm. in diameter and 6 mm. in thickness, with 6 holes, each about 24 mm. in diameter, equidistant from the center of the plate and equally spaced from one another.

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* A suitable apparatus is available from Van-Kel Industries, Inc., P.O. Box 167, Livingston, NJ 07034, or from Hanson Research Corp., 10945 Nestle Avenue, Northridge, CA 91324.

Attached by screws to the under surface of the lower plate is 10-mesh No. 23 (0.65 mm.) W. and M. gauge woven stainless steel wire cloth. The glass tubes and the upper plastic plate are secured in position at the top by means of a stainless steel plate, about 9 cm. in diameter and 1 mm. in thickness, having 6 perforations, each about 20 mm. in diameter, which coincide with those of the upper plastic plate and the upper open ends of the glass tubes. A central shaft about 8 cm. in length, the upper end of which terminates in an eye through which a string or wire may be inserted, is attached to the stainless steel plate. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the 2 plastic plates and the steel plate.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks**—Each tube is provided with a slotted and perforated cylindrical disk 9.5 ± 0.15 mm. thick and 20.7 ± 0.15 mm. in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five 2-mm. holes extend between the ends of the cylinder, one of the holes being through the cylinder axis and the others parallel with it equally spaced on a 6-mm. radius from it. Equally spaced on the sides of the cylinder are four notches that form V-shaped planes that widen to 9.5 mm. on the top of the cylinder along a chord of the top surface and with the center point along this chord being 2.55 mm. from the side of the cylinder. Each notch creates a 1.60-mm. square opening on the surface of the cylinder to be placed downward in the tube. All surfaces of the disk are smooth.

Procedure

Uncoated Tablets—Place 1 tablet in each of the six tubes of the basket, add a disk to each tube, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid unless another fluid is specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets—Place 1 tablet in each of the six tubes of the basket and, if desired, immerse the latter in water at room temperature for 5 minutes to wash off any soluble, external coating. Then add a disk to each tube, and operate the apparatus, using simulated gastric fluid T.S.† maintained at 37 ± 2° as the immersion fluid. After 30 minutes, lift the basket from the fluid, and observe the tablets. If the tablets have not disintegrated completely, substitute simulated intestinal fluid T.S.† maintained at 37 ± 2° as the immersion fluid, and continue the test for a total period of time, including previous exposure to water and simulated gastric fluid T.S., equal to the time limit specified in the individual monograph plus 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Enteric-Coated Tablets—Place 1 tablet in each of the six tubes of the basket and, if desired, immerse the latter in water at room temperature for 5 minutes to wash off any soluble, external coating. Then operate the apparatus, using simulated gastric fluid T.S.† maintained at 37 ± 2° as the immersion fluid. One hour later, lift the basket from the fluid, and observe the tablets: the tablets show no distinct evidence of dissolution or disintegration. Then add a disk to each tube, and operate the apparatus, using simulated intestinal fluid T.S.† maintained at 37 ± 2° as the immersion fluid, for a period of time equal to 2 hours plus the time limit specified in the individual monograph, or, where only an enteric-coated tablet is recognized, for only the time limit specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets,* but omit the use of the disks. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets,* but omit the use of the disks. Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated completely.

** Disks meeting these specifications are obtainable from McKenzie and Company, Inc., P. O. Box 604, Pittsfield, MA 01201.

† Simulated gastric fluid T.S. and simulated intestinal fluid T.S. are prepared as directed in USP XVIII, without the use of enzymes, unless otherwise directed in an individual monograph.

THERMOMETERS

Thermometers suitable for National Formulary tests conform to the following designations and specifications of the American Society for Testing and Materials:

Mercury is the liquid in all of the types of thermometers listed below, and the column above the liquid is filled with nitrogen. The stem of each thermometer is made of suitable thermometer tubing and has a plain front and an enameled back. All graduation lines, figures, and letters are clear-cut on the glass stem and are uniformly well filled with insoluble colored pigment. An immersion line is etched on the front of each partial-immersion thermometer. The thermometers are thoroughly annealed so that they retain their accuracy after long-continued exposure to the highest temperature on the scale.

Details regarding the standardization of thermometers are given in ASTM Standards on Thermometers E1, American Society for Testing and Materials (1963).

Type	ASTM designation
I—For general purposes	E1 (1C)
II—For general purposes	E1 (2C)
III—For melting ranges of petrolatum and other Class III solids	E1 (14C)
IV—For determining kinematic viscosity	E1 (18C)
V—For determining the titer of fatty acids	E1 (36C)
VI—For boiling or distilling temperatures	E1 (7C)
VII—For boiling or distilling temperatures	E1 (8C)

Thermometer Specifications

Thermometer Type	I	II	III	IV	V	VI	VII
Temperature range	−20° to +150°	−5° to +300°	38° to 82°	34° to 42°	−2° to +68°	−2° to +300°	−2° to +400°*
Subdivisions	1°	1°	0.1°	0.1°	0.2°	1°	1°
Total length, mm.	322 ± 5	390 ± 5	377 ± 5	255 ± 5	405 ± 5	386 ± 5	386 ± 5
Stem diameter, mm.	6.0 to 7.0	6.0 to 7.0	6.0 to 7.0	6.0 to 7.0	6.0 to 7.0	6.0 to 7.0	6.0 to 7.0
Bulb diameter, mm.	5.0 to 6.0	5.0 to 6.0	5.0 to 6.0	5.0 to diam. of stem	5.5 to diam. of stem	5.0 to 6.0	5.0 to 6.0
Bulb length, mm.	19 to 25	10 to 15	18 to 28	25 to 35	15 to 25	10 to 15	10 to 15
Distance, in mm., from bottom of bulb to graduation at temperature indicated in parentheses	111 to 118 (0°)	100 to 110 (0°)	116 to 125 (40°)	135 to 150 (34.4°)	50 to 60 (−2°)	100 to 110 (0°)	25 to 45 (0°)
	268 to 287 (150°)	329 to 358 (300°)	315 to 335 (80°)	215 to 234 (42°)	350 to 370 (68°)	333 to 354 (300°)	333 to 354 (400°)
Longer graduation lines at each	5°	5°	0.5°	0.5°	1°	5°	5°
Graduations numbered at each	10°	10°	1°	1°	2°	10°	10°
Immersion	76 mm.	76 mm.	79 mm.	Total	45 mm.	Total	Total
Maximum scale error at any point†	0.5°	1°	0.1°	0.1°	0.2°	Up to 300°, 0.5°	Up to 370°, 1°

* Under certain test conditions, the temperature of the bulb of the thermometer may be 28° above the temperature indicated by the thermometer, and at an indicated temperature of 371° the temperature of the bulb is approaching a critical range in the glass. It is not advisable to use this thermometer under such conditions at indicated temperatures above 371° without checking the ice point.

† Special conditions of standardization for the seven types of thermometers are:

Types I and II are standardized at 76-mm. (3 in.) immersion at the following temperatures of the emergent mercury column, which are those likely to prevail in the use of Types I and II thermometers, respectively.

Standardization Temperature	Average Temperature of Emergent Mercury Column	
	Type I	Type II
−20°	8°	...
0°	18°	19°
50°	35°	...
75°	...	42°
100°	48°	...
150°	55°	61°
225°	...	73°
300°	...	80°

Type III is standardized at 40° and at 10° intervals for an emergent stem temperature of 25°. Type IV is standardized at 38° and at 41°. Type V is standardized at the ice point and at 15° intervals and at 65° for an emergent stem temperature of 25°. Type VI is standardized at the ice point, at 50° intervals, and at 300°. Type VII is standardized at the ice point, at 100° intervals, and at 370°.

THIAMINE ASSAY

The following procedure is provided for the determination of thiamine as an ingredient of official preparations containing other active constituents.

Special Solutions and Solvents—

1 Percent Potassium Ferricyanide Solution—Dissolve 1 g. of potassium ferricyanide in sufficient water to make 100 ml. Prepare fresh on the day of use.

Oxidizing Reagent—Mix 4 ml. of *1 Percent Potassium Ferricyanide Solution* with sufficient 3.5 *N* sodium hydroxide to make 100 ml. Use this solution within 4 hours.

Quinine Sulfate Stock Solution—Dissolve 10 mg. of quinine sulfate in sufficient 0.1 *N* sulfuric acid to make 1000 ml. Preserve this solution, protected from light, in a refrigerator.

Quinine Sulfate Standard Solution—Dilute 1 volume of *Quinine Sulfate Stock Solution* with 39 volumes of 0.1 *N* sulfuric acid. This solution fluoresces to approximately the same degree as the thiochrome obtained from 1 mcg. of thiamine hydrochloride and is used to correct the fluorophotometer at frequent intervals for variation in sensitivity from reading to reading within an assay. Prepare this solution fresh on the day of use.

Standard Thiamine Hydrochloride Stock Solution—Transfer about 25 mg. of USP Thiamine Hydrochloride Reference Standard, previously dried at 105° for 2 hours and accurately weighed, to a 1000-ml. volumetric flask, observing precautions to avoid absorption of moisture in weighing the dried Standard. Dissolve the weighed Standard in about 300 ml. of dilute alcohol solution (1 in 5) adjusted to a pH of 4.0 with diluted hydrochloric acid, and add the acidified, dilute alcohol to volume. Store in a light-resistant container, in a refrigerator. Prepare this stock solution fresh each month.

Standard Preparation—Pipet a volume of *Standard Thiamine Hydrochloride Stock Solution,* equivalent to 100.0 mcg. of USP Thiamine Hydrochloride Reference Standard, into a 100-ml. volumetric flask, and dilute to volume with 0.2 *N* hydrochloric acid. Dilute 10.0 ml. of this solution to 50.0 ml. with 0.2 *N* hydrochloric acid. Each ml. of the resulting *Standard Preparation* contains 0.2 mcg. of USP Thiamine Hydrochloride Reference Standard.

Assay Preparation—Place in a suitable volumetric flask sufficient of the material to be assayed, accurately weighed or measured by volume as directed, such that when diluted to volume with 0.2 *N* hydrochloric acid the resulting solution will contain about 100 mcg. of thiamine hydrochloride (or mononitrate) in each ml. If the sample is difficultly soluble, the solution may be heated on a steam bath, and then cooled and diluted to volume. Dilute 5.0 ml. of this solution, quantitatively and stepwise, using 0.2 *N* hydrochloric acid, to an estimated concentration of 0.2 mcg. of thiamine hydrochloride (or mononitrate) per ml.

Procedure—Into each of three or more tubes (or other suitable vessels), of about 40-ml. capacity, pipet 5.0 ml. of the *Standard Preparation.* To each of two of these tubes add rapidly (within 1 to 2 seconds), with mixing, 3 ml. of the *Oxidizing Reagent,* and within 30 seconds add 20.0 ml. of isobutyl alcohol, then mix vigorously for 90 seconds by shaking the capped tubes manually, or by bubbling a stream of air through the mixture. Prepare a blank in the remaining tube of the standard by substituting for the *Oxidizing Reagent* an equal volume of 3.5 *N* sodium hydroxide and proceeding in the same manner.

Into each of three or more similar tubes pipet 5.0 ml. of the *Assay Preparation.* Treat these tubes in the same manner as directed for the tubes containing the *Standard Preparation.*

To each of the six or more tubes add 2.0 ml. of dehydrated alcohol, swirl for a few seconds, allow the phases to separate, and decant or draw off about 10 ml. of the clear, supernatant isobutyl alcohol solution into standardized cells, then measure the fluorescence in a suitable fluorophotometer having an input filter of narrow transmittance range with a maximum at about 365 $m\mu$ and an output filter of narrow transmittance range with a maximum at about 435 $m\mu$.

Calculation—The number of mcg. of $C_{12}H_{17}ClN_4OS.HCl$ in each 5 ml. of the *Assay Preparation* is given by the formula $(A - b)/(S - d)$, in which A is the average of the fluorophotometer readings of the portions of the *Assay Preparation* treated with the *Oxidizing Reagent,* b is the fluorophotometer reading of the *Assay Preparation* blank, S is the average of the fluorophotometer readings of the portions of the *Standard Preparation* treated with the *Oxidizing Reagent,* and d is the fluorophotometer reading of the *Standard Preparation* blank.

Calculate the quantity, in mg., of $C_{12}H_{17}ClN_4OS.HCl$ (thiamine hydrochloride) in the assay material on the basis of the aliquots taken. Where indicated, the quantity, in mg., of $C_{12}H_{16}N_4OS.HNO_3$ (thiamine mononitrate) may be calculated by multiplying the quantity of $C_{12}H_{17}ClN_4OS.HCl$ found by 0.9706.

TIMED-RELEASE TABLETS AND CAPSULES—IN VITRO TEST PROCEDURE

The procedure and apparatus described in this Chapter may be useful, either directly or as a point of reference, in establishing suitable test criteria to assure product uniformity of most timed-release* tablets and capsules. The procedure is presented for its value as a routine control test method and is not intended to establish official specifications for any preparation recognized in the monographs section of this National Formulary. Through actual experience it may be determined that the described apparatus and procedure are not suitable for testing certain types of products.

Caution: This *in vitro* method is not designed to assure or measure safety or effectiveness, both of which must be determined through comprehensive *in vivo* studies and clinical evaluation. From the *in vivo* test data and clinical evaluation, however, suitable *in vitro* release limits may be established.

Apparatus—The apparatus† consists of a horizontal rotating shaft to which are attached clamps to hold round screw-capped bottles,‡ each approximately 150 mm. long and having an internal diameter of approximately 30 mm. The clamps are designed so that the long axis of the bottle is at a right angle to the axis of the shaft and they are adjusted so that the distance between the axes is about 47.5 mm. The rotating shaft with the attached bottles is mounted in a constant-temperature water bath. The shaft is connected by a chain drive to an electric motor equipped with a speed-regulating device capable of rotating at speeds varying from 6 r.p.m. to 50 r.p.m.

Extracting Fluid pH	Simulated Gastric Fluid T.S., ml.	Simulated Intestinal Fluid T.S., ml.
1.2	100	0
2.5	46	54
4.5	39	61
7.0	17.5	82.5
7.5	0	100

Extracting Fluids**—Prepare 100 ml. each of five extracting fluids by mixing the volumes of simulated gastric fluid T.S. and simulated intestinal fluid T.S. indicated in the accompanying table, and adjust each fluid to the appropriate pH (±0.1) with either test solution as necessary.

Procedure—[NOTE: The speed of rotation; time intervals for assay; the pH, composition, and volume of the extracting fluids; size and position of the bottles; method of temperature control; and other conditions may be varied for testing convenience and to achieve the desired correlation with the *in vivo* studies and clinical evaluation; provided that any such variations are applied uniformly and consistently in all tests of a particular preparation. In some cases, it may be more appropriate to assay the filtered extract rather than the residue.]

Place a suitable number of tablets or capsules in each of five bottles, and to each bottle add 60 ml. of *pH 1.2 Extracting Fluid*, previously warmed to 37°. Cap the bottles tightly and place them in the clamps on the shaft of the apparatus. Rotate the bottles at 40 ± 2 revolutions per minute in the water bath maintained at 37° ± 0.5°.

At the end of 1 hour, stop the rotor and remove all bottles from the apparatus. Individually decant the *pH 1.2 Extracting Fluid* from the five bottles through separate 40-mesh metal screens, retaining as much residue in four of the bottles as is conveniently possible. From each of four screens, quantitatively return any decanted residue to its respective original bottle by inverting the screen on a wide-stemmed funnel and washing the residue into the bottle with 60 ml. of *pH 2.5 Extracting Fluid*, previously warmed to 37°. Cap the four bottles tightly, return them to the apparatus, and continue to rotate. Quantitatively transfer the contents of the fifth bottle onto a 40-mesh metal screen using 25 to 30 ml. of water. (The transfer may be conveniently accomplished by directing a stream of water from a wash bottle onto the inner walls of the bottle inverted at an angle over the screen.) Retain the residue for assay.

At the end of 2 hours total rotation time, stop the rotor and remove all bottles from the apparatus. Collect the residue from one bottle on a screen as previously described, and retain the residue for assay. Decant the *pH 2.5 Extracting Fluid* from the other three bottles, and return any decanted residue to its respective original bottle using 60 ml. of *pH 4.5 Extracting Fluid*, previously warmed to 37°. Cap the three bottles tightly, return them to the apparatus, and continue to rotate.

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* As understood here, *timed-release* would include those tablets and capsules variously known as "delayed-action," "extended-release," "prolonged-action," "sustained-action," or "repeat-action," but would not include tablets specifically identified as "enteric-coated."

† Available from E. O. Menold Sheet Metal Company, Fifth and Powhatan Ave., Lester, PA 19113.

‡ Available from Owens-Illinois Glass Co., 405 Madison Ave., Toledo, Ohio 43604. 3 oz. o'flow round, 35-440-405 finish (Miles Laboratories, Inc. design).

** Simulated gastric fluid T.S. and simulated intestinal fluid T.S. are prepared as directed in USP XVIII, without the use of enzymes, unless otherwise directed in an individual monograph.

At the end of 3.5 hours total rotation time, stop the rotor and remove all bottles from the apparatus. Collect the residue from one bottle on a screen as previously described, and retain the residue for assay. Decant the *pH 4.5 Extracting Fluid* from the other two bottles, and return any decanted residue to its respective original bottle using 60 ml. of *pH 7.0 Extracting Fluid*, previously warmed to 37°. Cap the two bottles tightly, return them to the apparatus, and continue to rotate.

At the end of 5 hours total rotation time, stop the rotor and remove both bottles from the apparatus. Collect the residue from one bottle on a screen as previously described, and retain the residue for assay. Decant the *pH 7.0 Extracting Fluid* from the remaining bottle, and return any decanted residue to the original bottle using 60 ml. of *pH 7.5 Extracting Fluid*, previously warmed to 37°. Cap the bottle tightly, return it to the apparatus, and continue to rotate.

At the end of 7 hours total rotation time, stop the rotor and remove the remaining bottle from the apparatus. Collect the residue on a screen as previously described, and retain the residue for assay.

Proceed to assay the residue on each screen by an appropriate procedure.

TITRIMETRY

Direct Titrations—Direct titration is the treatment of a soluble substance, contained in solution in a suitable vessel (the titrate), with an appropriate standardized solution (the titrant), the end-point being determined instrumentally or visually with the aid of a suitable indicator.

The titrant is added from a suitable buret and is so chosen, with respect to its strength (normality), that the volume added is between 30 percent and 100 percent of the rated capacity of the buret. (Note—When less than 10 ml. of titrant is required, a suitable microburet is to be used.) The end-point is approached directly but cautiously, and finally the titrant is added dropwise from the buret in order that the final drop added will not over-run the endpoint. The quantity of the substance being titrated may be calculated from the volume and the normality factor of the titrant and the equivalence factor for the substance given in the individual monograph.

Residual Titrations—Some National Formulary assays require the addition of a measured volume of a volumetric solution, in excess of the amount actually needed to react with the substance being assayed, the excess of this solution then being titrated with a second volumetric solution. This constitutes a residual titration and is known also as a "back titration." The quantity of the substance being titrated may be calculated from the difference between the volume of the volumetric solution originally added and that consumed by the titrant in the back titration, due allowance being made for the respective normality factors of the two solutions, and the equivalence factor for the substance given in the individual monograph.

In many such assays it is further specified that a *residual blank titration* be performed, wherein the required procedure is repeated in every detail except that the substance being assayed is omitted. In such instances, the actual volume of titrant equivalent to the substance being assayed is the difference between the volume consumed in the residual blank titration and that consumed in the titration with the substance present. The corrected volume so obtained is used in calculating the quantity of the substance being titrated, in the same manner as prescribed in the preceding paragraph.

Chelometric Titrations—Simple, direct titrations of some polyvalent cations are possible by use of reagents with which the cations form complexes. The titration of the calcium ion by this means is particularly advantageous, in comparison to the oxalate precipitation method previously used for National Formulary purposes. The success of complexometry depends in large measure upon the indicator chosen. Often the color change of an indicator can be improved by the addition of a screening agent.

Indicator and Potentiometric End-Point Detection—The simplest and most convenient means by which the equivalence point, i.e., the point at which the stoichiometric analytical reaction is complete, may be determined is with the use of indicators. These chemical substances, usually colored, respond to changes in solution conditions before and after the equivalence point by exhibiting color changes which may be taken visually as the end-point, a reliable estimate of the equivalence point.

A very useful method of end-point determination results from the use of electrochemical measurements. If an indicator electrode, sensitive to the concentration of the species undergoing titrimetric reaction, and a reference electrode, whose potential is insensitive to any dissolved species, are immersed in the titrate to form a galvanic cell, then the potential difference between the electrodes may be sensed by a pH meter and used to follow the course of the reaction. Such a series of measurements when plotted correctly (*vis* for an acid-base titration, pH *vs.* ml. of titrant added; for a precipitimetric, complexometric or oxidation-reduction titration, millivolts *vs.* ml. of titrant added), a sigmoid curve results with a rapidly changing portion in the vicinity of the equivalence point. The mid-point of this linear vertical portion or the inflection point may be taken as the end-point.

Two types of automatic titrators are available. The first is one which carries out titrant addition automatically and records the electrode potential differences during the course of titration as the expected sigmoid curve. In the second type, titrant addition is performed automatically until a pre-set potential or pH, representing the end-point, is reached, at which point the titrant addition ceases.

It is clear that the electrode system choice is very important in potentiometric titrations. Acceptable electrode systems are summarized in the accompanying table.

Titration in Nonaqueous Solvents—Acids and bases have long been defined as substances which furnish, when dissolved in water, hydrogen and hydroxyl ions, respectively. This definition, introduced by Arrhenius, fails to recognize the fact that properties characteristic of acids or bases may be developed also in other solvents. A more generalized definition is that of Brönsted, who defines an acid as a substance which furnishes protons, and a base as a substance which combines with protons. Even broader is the definition of Lewis, who defines an acid as any material that will accept an electron pair, a base as any material that will donate an electron pair, and neutralization as the formation of a coordination bond between an acid and a base.

The apparent strength of an acid or base is determined by the extent of its reaction with a solvent. In water solution all strong acids appear equally strong because they react with the solvent to undergo almost complete conversion to hydronium ion and the acid anion (leveling effect). In a weakly protophilic solvent such as acetic acid the extent of formation of the acetonium ion shows that the order of decreasing strength for acids is perchloric, hydrobromic, sulfuric, hydrochloric, and nitric (differentiating effect).

Acetic acid reacts incompletely with water to form hydronium ion and is, therefore, a weak acid. In contrast, it dissolves in a base such as ethylenediamine, and reacts so completely with the solvent that it behaves as a strong acid. The same holds for perchloric acid.

This leveling effect is observed also for bases. In sulfuric acid almost all bases appear to be of the same strength. As the acid properties of the solvent decrease in the series sulfuric acid, acetic acid, phenol, water, pyridine, and butylamine, the bases become progressively weaker until all but the strongest have lost their basic properties. In order of decreasing strength, the strong bases are sodium 2-aminoethoxide, potassium methoxide, sodium methoxide, and lithium methoxide.

Many water-insoluble compounds acquire enhanced acidic or basic properties when dissolved in organic solvents. Thus the choice of the appropriate solvent permits the determination of a variety of such materials by nonaqueous titration. Further, depending upon which part of a compound is the physiologically active moiety, it is often possible to titrate that part by proper selection of solvent and titrant. Pure compounds can be titrated directly, but it is often necessary to isolate the active ingredient in pharmaceutical preparations from interfering excipients and carriers.

The types of compounds that may be titrated as acids include acid halides, acid anhydrides, carboxylic acids, amino acids, enols such as barbiturates and xanthines,

Potentiometric Titration Electrode Systems

Titration	Indicating Electrode	Equation*	Reference Electrode	Applicability**
Acid-base	Glass	$E = k + 0.0591 \text{ pH}$	Calomel or silver-silver chloride	Titration of acids and bases
Precipitimetric (Silver)	Silver	$E = E^\circ + 0.5491 \log [\text{Ag}^+]$	Calomel	Titration with or of silver involving halides or thiocyanate
Chelometric	Mercury-Mercury(II)	$E = E^\circ = 0.0296 \log k' - \text{pM}$	Calomel	Titration of various metals (M), e.g., Mg^{+2}, Ca^{+2}, Al^{+3}, Bi^{+3}, with EDTA
Oxidation-reduction	Platinum	$E = E^\circ + \frac{0.0591}{11} \log \frac{[\text{ox}]}{[\text{red}]}$	Calomel or silver-silver chloride	Titrations with arsenite, bromine, cerate, dichromate, hexacyanoferrate(III), iodate nitrite, permanganate, thiosulfate

* Appropriate form of Nernst equation describing the indicating electrode system: k = glass electrode constant; k' = constant derived from Hg-Hg(II)-EDTA equilibrium; M = any metal undergoing EDTA titration; [ox] and [red] from the equation, $\text{ox} + ne \rightleftharpoons \text{red}$.

** Listing is representative but not exhaustive.

imides, phenols, pyrroles, and sulfonamides. The types of compounds that may be titrated as bases include amines, nitrogen-containing heterocyclic compounds, oxazolines, quaternary ammonium compounds, alkali salts of organic acids, alkali salts of weak inorganic acids, and some salts of amines. Many salts of halogen acids may be titrated in acetic acid or acetic anhydride after the addition of mercuric acetate, which removes halide ion as the unionized mercuric halide complex and introduces the acetate ion.

In the titration of a basic compound, a volumetric solution of perchloric acid in glacial acetic acid is preferred, although perchloric acid in dioxane is used in special cases. The glass-calomel electrode system is useful in this case. In acetic acid solvent this electrode system functions as predicted by theory.

In the titration of an acidic compound, two classes of titrant are available: the alkali metal alkoxides and the tetraalkylammonium hydroxides. A volumetric solution of sodium methoxide in a mixture of methanol and benzene is used frequently, although lithium methoxide in methanol-benzene solvent is used for those compounds yielding a gelatinous precipitate on titration with sodium methoxide.

The alkali error limits the use of the glass electrode as an indicating electrode in conjunction with alkali metal alkoxide titrants, particularly in basic solvents. Thus, the antimony indicating electrode, though somewhat erratic, is used in such titrations. The use of quaternary ammonium hydroxide compounds, e.g., tetra-*n*-butylammonium hydroxide, trimethylhexadecylammonium hydroxide (in benzene-methanol or isopropanol), has two advantages over the other titrants in that (a) the tetraalkylammonium salt of the titrated acid is soluble in the titration medium, and (b) the convenient and well-behaved glass-calomel electrode may be used to conduct potentiometric titrations.

Because of interference by carbon dioxide, solvents for acidic compounds must be protected from excessive exposure to the atmosphere by a suitable cover or by an inert atmosphere during the titration. Absorption of carbon dioxide may be determined by performing a blank titration. The blank should not exceed 0.01 ml. of 0.1 *N* sodium methoxide per ml. of solvent.

The end-point may be determined visually by color change, or potentiometrically, as indicated in the individual monograph. If the calomel reference electrode is used, it is advantageous to replace the aqueous potassium chloride salt bridge with 0.1 *N* lithium perchlorate in glacial acetic acid for titrations in acidic solvents or potassium chloride in methanol for titrations in basic solvents.

The more useful systems for titration in nonaqueous solvents are listed in the table on page 905.

CRUDE VEGETABLE DRUGS—METHODS FOR SAMPLING AND ANALYSIS

I. Sampling from Original Containers—(*a*) It is recommended that gross samples of crude vegetable drugs in which the component parts are 1 cm. or less in any dimension, and all powdered or ground drugs, be taken by means of a sampler which removes a core from the top to the bottom of the container, not less than 2 cores being taken in opposite directions; that when the total weight of the drug to be sampled is less than 100 kg. (220 pounds) at least 250 g. shall constitute an *official sample.* When the total weight of the drug to be sampled is in excess of 100 kg., take repeated samples by the above method, and according to the schedule given below, mix and quarter, reject 2 of the diagonal quarters, combine and carefully mix the remaining 2 quarters and again subject the drug to a quartering process in the same manner until 2 of the quarters weigh at least 250 g., which latter quarters constitute an *official sample.*

(*b*) It is recommended that gross samples of crude vegetable drugs in which the component parts are over 1 cm. in any dimension be taken by hand. When the total weight of the drug to be sampled is less than 100 kg. at least 500 g. constitutes an *official sample,* this being taken from different parts of the container or containers. When the total weight of the drug to be sampled is in excess of 100 kg., take repeated samples by the above method and according to the schedule below, mix and quarter, reject 2 of the diagonal quarters, combine and carefully mix the remaining 2 quarters, and again subject the drug to a quartering process in the same manner until 2 of the quarters weigh not less than 500 g., which latter quarters constitute an *official sample.*

Schedule Recommended for Sampling

Number of Packages in Shipment	Number of Packages to Be Sampled
1 to 10	1 to 3
10 to 25	3 to 4
25 to 50	4 to 6
50 to 75	6 to 8
75 to 100	8 to 10

When over 100, the total number sampled is not less than 10.

(*c*) When the total weight of a drug to be sampled is less than 10 kg., it is recommended that the above methods be followed but that somewhat smaller quantities be withdrawn; in no case should the final *official sample* weigh less than 125 g.

(*d*) In addition to the withdrawing of *official samples* according to methods *a*, *b*, and *c*, the *official sample* may consist of the total amount of a direct purchase made by federal, state, or municipal food and drug act enforcement officials.

II. Foreign Organic Matter in Whole Crude Vegetable Drugs—Withdraw from 25 to 500 g. from the *official sample*, spread out in a thin layer, and separate the foreign organic matter by hand as completely as possible. Weigh it and determine the percent of foreign organic matter, calculated upon the weight of drug taken. Use the maximum quantity of sample for coarse or bulky drugs.

III. Preparation of Crude Vegetable Drugs for Analysis—The following method is to be used where specific directions are not otherwise given in the text: Withdraw as much as may be necessary of the *official sample* by quartering, taking care to see that the portion is representative of the gross sample. In the case of unground or unpowdered drugs grind the withdrawn sample so that it will pass through a No. 20 standard mesh sieve. If the sample cannot be ground, reduce it to as fine a state as possible. Mix by rolling it on paper or sampling cloth, spread it out in a thin layer and withdraw the portion for analysis. The disintegration of semisolid drugs may be facilitated by the use of a meat grinder or a similar apparatus.

IV. Total Ash in Crude Vegetable Drugs—Accurately weigh a quantity of the ground drug, representing from 2 to 4 g. of the air-dried material, in a tared crucible and incinerate at a low temperature, not to exceed very dull redness, until free from carbon, and determine the weight of the ash. If a carbon-free ash cannot be obtained in this way, exhaust the charred mass with hot water, collect the insoluble residue on an ashless filter paper, incinerate the residue and filter paper until the ash is white or nearly so, then add the filtrate, evaporate it to dryness, and heat the whole to a low redness. If a carbon-free ash cannot be obtained in this way, cool the crucible, add 15 ml. of alcohol, break up the ash with a glass rod, burn off the alcohol, and again heat the whole to a low redness. Finally determine the weight of the ash. Calculate the percentage of total ash from the weight of the drug taken.

V. Acid-insoluble Ash in Crude Vegetable Drugs—Boil the ash obtained under paragraph IV with 25 ml. of diluted hydrochloric acid for 5 minutes, collect the insoluble matter on a tared Gooch crucible or ashless filter, wash with hot water, ignite, and weigh. Determine the percent of acid-insoluble ash calculated from the weight of drug taken.

Moisture

VI. Preparation of Sample—In the case of unground or unpowdered drugs, prepare about 10 g. of the *official sample* by cutting, granulating or shredding, so that the parts are about 3 mm. in thickness. Seeds or fruits smaller than 3 mm. should be cracked. High-speed mills should not be used for preparing the sample and care should be taken that no appreciable amount of moisture is lost during the preparation and that the portion taken is representative of the *official sample.*

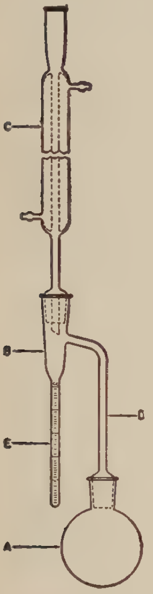
VII. Moisture Method for Drugs Containing No Constituents Volatile at 105°—Accurately weigh about 10 g. of the drug as prepared under paragraph VI in a tared evaporating dish. Dry at 105° for 5 hours and weigh. Continue the drying and weighing at 1-hour intervals until the loss is not more than 0.25 percent in 1 hour's drying.

VIII. Moisture Method for Drugs Containing Ether-soluble Constituents Volatile at 105°—Proceed as under paragraph VII. Determine the volatile ether-soluble extractive (paragraph XV), and subtract the percentage of volatile ether-soluble extractive from the percentage lost during drying. The difference represents the percentage of moisture.

IX. Moisture Method by Toluene Distillation—*Apparatus*—The apparatus (see illustration) required consists of a glass flask, *A*, connected by means of a trap, *B*, to a reflux condenser, *C*. All joints in the apparatus are of ground glass. The flask has a capacity of 500 ml., is either of the short-neck, round-bottom type or of the conical type, and made of resistant glass.

The length of the trap is between 235 and 240 mm., and the distance between the connecting tube, *D*, and the receiving tube, *E*, is between 45 and 55 mm. The internal diameter of the connecting tube is between 9 and 11 mm. and where sealed to the body of the trap is inclined at an angle of 15° from the horizontal. The length of the cylindrical portion of the receiving tube is between 146 and 156 mm., and the internal diameter of the neck of the trap is between 22 and 24 mm. The receiving tube is graduated to contain 5 ml. and is subdivided into 0.1-ml. divisions, each 1-ml. line being numbered from 5 ml. at the top. The error in any indicated capacity may not be greater than 0.05 ml.

The jacket of the condenser is approximately 400 mm. in length, and the inner tube of the condenser should have an external diameter between 9.5 and 12.7 mm. The end of the condenser that is inserted into the trap is ground off at an angle of 30° from the vertical axis, and when inserted into the trap, the tip of the condenser is about 7 mm. above the surface of the liquid in the trap after the distillation conditions have been established.



Toluene Moisture Apparatus

The source of heat is preferably an electric heater with rheostat control or an oil bath. The upper portion of the flask and the connecting tube may, if desired, be wrapped with asbestos paper or asbestos cord.

The receiving tube and the condenser must be chemically clean in order to permit the sharp separation of water. Clean these parts with chromic acid cleansing mixture, thoroughly rinse with water, and dry in an oven.

First saturate the toluene used in the moisture determination with water by shaking with a small quantity of water, separate it from the excess water, and distil the toluene.

Determination—Place in the dry flask a quantity of the substance, weighed accurately to the nearest centigram, which is estimated will yield from 2 to 4 ml. of water. If the substance is of a pasty character, it is best weighed in a boat of metal foil of a size that will just pass through the neck of the flask. If the substance is likely to cause bumping, add enough dry, washed sand to cover the bottom of the flask, or a number of capillary melting-point tubes, about 100 mm. in length, sealed at the upper end. Place about 200 ml. of toluene in the flask, connect the apparatus as illustrated, and fill the receiving tube, *E*, with toluene poured through the top of the condenser. Heat the flask gently for 15 minutes, and when the toluene begins to boil, distil at the rate of about 2 drops per second until most of the water has passed over; then increase the rate of distillation to about 4 drops per second. When the water has apparently all distilled over, rinse the inside of the condenser tube with toluene while brushing down the tube with a tube brush attached to a copper wire and saturated with toluene. Continue the distillation for 5 minutes, then remove the heat and allow the receiving tube to cool to room temperature. If any droplets of water adhere to the walls of the receiving tube, force them down with a rubber band wrapped around a copper wire and wet with toluene. When the water and toluene have separated completely, read the volume of water and calculate the percentage that was present in the substance.

X. Crude Fiber—Exhaust a weighed quantity of the prepared drug (paragraph III), representing about 2 g. of the drug, with ether or use the residue from the determination of the volatile ether-soluble extractive (paragraph XV). Add 200 ml. of boiling 1.25 percent sulfuric acid solution, to the ether-exhausted drug, in a 500-ml. flask, and connect the flask with a reflux condenser, the tube of which passes only a short distance below the rubber stopper, into the flask. Heat the mixture to boiling and continue the boiling exactly 30 minutes. Then filter through a linen or hardened-paper filter and wash the residue on the filter with boiling water until no longer acid. Rinse the residue back into the flask with 200 ml. of boiling sodium hydroxide solution, adjusted to exactly 1.25 percent by titration and free from sodium carbonate. Again heat the mixture to boiling and continue the boiling exactly 30 minutes under the reflux condenser as described under the treatment with acid, then rapidly filter through a tared filter, wash the residue with boiling water until the last washing is neutral, dry it at 105° until of constant weight, and note the weight. Now completely incinerate the dried residue and weigh the ash: the loss in weight is considered to be the weight of the crude fiber.

NOTE: Continue the boiling with acid and alkali *exactly* 30 minutes from the time the liquid (which is cooled below the boiling point by adding it to the cold flask) again boils. After the solution has been brought to boiling, adjust the heat just low enough to maintain boiling. During the boiling, gently rotate the flask from time to time to catch any particles which may adhere to the walls of the flask. A slow current of air introduced into the flask during the boiling operation will be very helpful to keep down excessive frothing.

Extractives

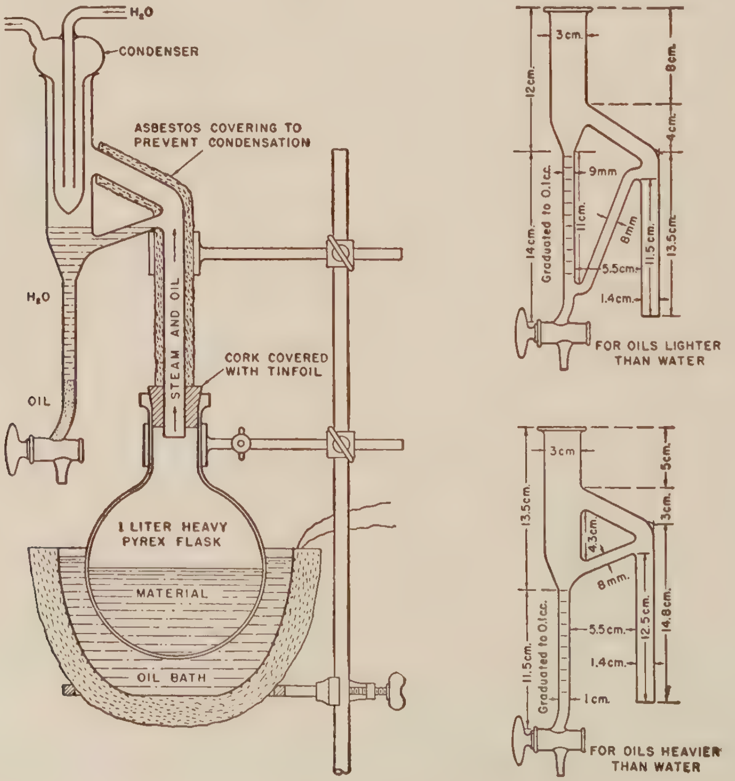
XI. Alcohol-soluble Extractive—Weigh accurately 2 g. of the prepared drug (paragraph III) into a dried and tared paper extraction thimble, using a glass-stoppered weighing bottle as the container, and place 200 mg. of sodium hydroxide in the receiving flask. Extract the drug in a continuous extraction apparatus with alcohol, during 5 hours. Dry the insoluble residue at 105° for 30 minutes and weigh. Determine the moisture in the drug by the *Toluene Distillation Method* (paragraph IX), calculate the weight of moisture in the quantity of drug taken for the test, and subtract it from the original weight of the drug taken for the test. The difference between this result and the weight of the residue determined as directed above represents the amount of alcohol-soluble extractive.

XII. Diluted Alcohol-soluble Extractive—Macerate about 2 g. of the prepared drug (paragraph III), accurately weighed, in about 70 ml. of diluted alcohol in a suitable flask. Shake the mixture during 8 hours at 30-minute intervals and then allow it to stand for 16 hours without shaking. Filter and wash the flask and residue with small portions of diluted alcohol, passing the washings through the filter, until the filtrate measures 100.0 ml. Evaporate a 50.0-ml. aliquot of this filtrate to dryness in a suitable tared dish on a water bath and dry at 105° to constant weight. Calculate the percentage of this extractive from the weight of drug taken.

XIII. Solvent Hexane-soluble Extractive—Extract completely about 2 g. of the prepared drug (paragraph III), accurately weighed, by subjecting it during 20 hours to the action of solvent hexane in a continuous extraction apparatus. Transfer the hexane solution to a tared porcelain dish and allow it to evaporate spontaneously. Then dry it over phosphorus pentoxide for 18 hours and weigh. Calculate the percentage of this extractive from the weight of drug taken.

XIV. Nonvolatile Ether-soluble Extractive—Proceed as directed under *Volatile Ether-soluble Extractive* (paragraph XV). The weight of the extract after drying in a desiccator and then at 105° until of constant weight represents the nonvolatile portion of the extract.

XV. Volatile Ether-soluble Extractive—Extract 2 g. of the prepared drug (paragraph III), dried over phosphorus pentoxide for not less than 12 hours and accurately weighed, with absolute ether for 20 hours in a continuous extraction apparatus. Transfer the ether solution to a



Volatile Oil Apparatus

tared porcelain dish and allow it to evaporate spontaneously. Then dry it over phosphorus pentoxide during 18 hours and weigh the total ether extract. Now heat the extract gradually up to 105° until the weight becomes constant: the loss in weight represents the volatile portion of the extract.

XVI. Water-soluble Extractive—Proceed as directed under paragraph XII, using water instead of diluted alcohol.

XVII. Volatile Oil Determination—Set up an apparatus as shown in the illustration, using an appropriate volatile oil trap as illustrated, page 888. Use a suitable oil bath for heating.

Determination—(*A*) *For Products Containing But Little Starch or Mucilage*—Coarsely comminute a sufficient quantity of the drug to yield from 1 ml. to 3 ml. of volatile oil. Small seeds or fruits or broken leaves of herbs ordinarily do not need comminution. Very fine powders are to be avoided. If this is not possible, it may be necessary to mix them with purified sawdust or purified sand. Place a suitable quantity of the drug, accurately weighed, in the flask and fill it one-half with water. Attach the condenser and the proper separator. Glass beads or a glass rod may be added to prevent bumping. Boil the contents of the flask, using a suitable source of heat to maintain gentle boiling for two hours, or until the volatile oil has been completely separated from the drug and no longer collects in the graduated tube of the separator.

If a proper quantity of the volatile oil has been obtained in the graduated tube of the separator, it can be read to tenths of a ml., and the volume of volatile oil from each 100 g. of drug can be calculated from the weight of the drug taken. The graduations on the separator "for oils heavier than water" are so placed that oil remains below the aqueous condensate which automatically flows back into the flask.

(*B*) *For Products Containing Considerable Starch or Mucilage*—Exhaust an accurately weighed quantity of the drug with alcohol or ether in an automatic extractor, transfer the extract to a suitable container and evaporate the solvent from the extract, using as little heat as possible and a gentle current of air. When the odor of the solvent is no longer perceptible, mix the extract with a quantity of dry, purified sawdust, transfer the mixture to the flask used for volatile oil determination, add a suitable amount of water, and proceed as directed under (*A*).

(*C*) *For Fluid Preparations Containing Volatile Oil*—Place a suitable quantity of the fluid preparation into the flask of the apparatus used for volatile oil determination and evaporate the solvent, using as little heat as possible and a current of air, until the odor of the solvent is no longer perceptible, add water to the flask and proceed as directed under (*A*).

VISCOSITY

Viscosity is a property of liquids that is closely related to the resistance to flow. It is defined in terms of the force required to move one plane surface past another under specified conditions when the space between is filled by the liquid in question. It can be considered more simply as a relative property where water is the reference material and all viscosities are expressed in terms of the viscosity of pure water at 20°. The latter quantity is given as (very nearly) one *centipoise,* and a material ten times as viscous as water at this temperature has a viscosity of ten centipoises. The basic unit is the *poise;* for convenience, the *centipoise* (1 poise = 100 centipoises) is employed. The specifying of temperature is important because viscosity usually changes with temperature; in general, viscosity decreases as temperature is raised. While on the absolute scale viscosity is measured in poises or centipoises, it is more convenient to use the kinematic scale, in which the units are *stokes* and *centistokes* (1 stoke = 100 centistokes). The kinematic viscosity is obtained from the absolute viscosity by dividing the latter by the density of the liquid at the same temperature, *i.e.,* Kinematic viscosity = (absolute viscosity)/(density). The sizes of the units are such that viscosities in the ordinary ranges are conveniently expressed in centipoises and centistokes. The approximate viscosity in centistokes at room temperature of ether is 0.2; of water, 1; of kerosene, 2.5; of mineral oil, 20 to 70; and of honey, 10,000.

Viscosity can be determined by any method that will measure the resistance to shear offered by the liquid. For ordinary liquids, it is customary to determine the time required for a given sample of the liquid to flow, at a regulated temperature, through a small capillary tube, and to compare this time with that required by the reference liquid, such as water. If the viscosity of the reference liquid is known, the kinematic viscosity of the unknown liquid may be calculated. Many capillary tube viscosimeters have been devised, and nearly all are modifications of the Ostwald type. Several types are described, with directions for their use, by the American Society for Testing and Materials.*

Viscosity for commercial products is often expressed on arbitrary scales, and

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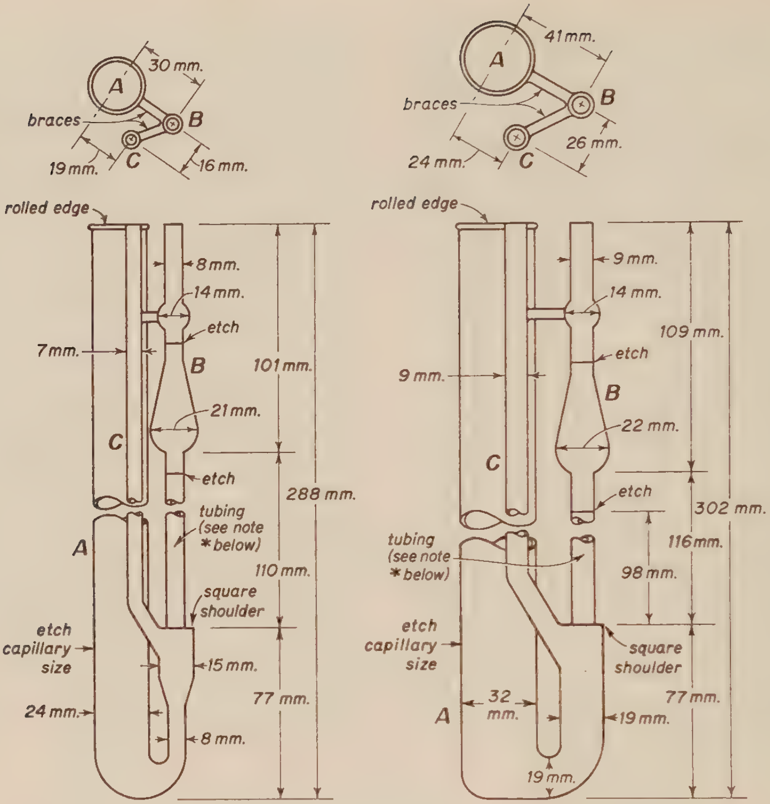
* ASTM, D-445; ASTM Standards on Petroleum Products and Lubricants.



Viscometer for Low Viscosity

* Precision bore capillary tubing 1.5 mm. i.d. for 15 cps., 1.8 mm. i.d. for 25 cps., 2.4 mm. i.d. for 100 cps., and 3.2 mm. i.d. for 400 cps. viscosities.

Viscometer for High Viscosity

* Precision bore capillary tubing 5.0 mm. i.d. for 1500 cps. and 6.0 mm. i.d. for 4000 cps. viscosities.

Viscometers Used in Determination of Viscosity of Cellulose Derivatives.

measured by empirical methods in special instruments. Thus semisolids are often examined by so-called rotary instruments, which measure the resistance to rotation of a cylinder, placed concentrically within another, the annular space being filled with the sample. The viscosity of oils is expressed on arbitrary scales, which vary from one country to another, there being several corresponding instruments. The most widely used are the Redwood No. I and No. II, the Engler, the Saybolt Universal, and the Saybolt Furol. The Redwood No. II and the Saybolt Furol viscosimeters are designed for extremely viscous oils, in that they have a wider capillary for the measurement. The Saybolt Furol readings are approximately one-tenth of those obtained on the same oil with the Saybolt Universal. Results for all the instruments are expressed in seconds of time required for outflow of a standard amount of liquid. Engler readings, however, may be reported as Engler degrees, and these latter are obtained by dividing the efflux time for the sample by the corresponding efflux time for water in the same instrument and at the same temperature. Standard temperatures are adopted as a matter of convenience. For the Saybolt instruments, measurements are usually made at 100° and 210° F. Redwood measurements may be at several temperatures up to 250° F., and Engler degrees are usually reported at 20° and 50° C.

The determination of kinematic viscosity with modern instruments is more rapid and convenient than with the use of the Saybolt and similar equipment. The Ostwald pipet type viscosimeter is therefore displacing the metal capillary variety, although the Saybolt, Redwood, and Engler scales have been retained. Kinematic viscosities determined in the Ostwald and Ubbelohde pipets are convertible to Saybolt and similar values by means of equations and conversion charts obtainable from the American Society for Testing and Materials.

Procedure for Cellulose Derivatives—Measurement of the viscosity of solutions of the high-viscosity types of cellulose derivatives is a special case, since they are too viscous for the commonly available viscosimeters. The Ubbelohde viscosimeter may be adapted as illustrated in the accompanying illustration (or ASTM, D-1347), to the measurement of the ranges of viscosity encountered in methylcellulose solutions.

Calibration of the Ostwald Type Viscosimeter—Determine the viscosimeter constant, *k*, for each viscosimeter by the use of an oil of known viscosity.† Place an excess of the oil (adjusted to 20 ± 0.1°) in the filling tube and transfer it to the orifice tube by gentle suction, taking care to prevent bubble formation in the liquid by keeping the air vent tube closed. Adjust the meniscus of the column of liquid in the orifice tube to the level of the top graduation line. Open both the vent and orifice tubes in order to permit the liquid to flow into the reservoir against atmospheric pressure. (Failure to open the vent tube before releasing the orifice tube will yield false values.) Record the time in seconds for the liquid to flow from the upper mark to the lower mark in the orifice tube.

Calculate the viscosimeter constant, *k*, from the equation $k = v/dt$, in which v is the known viscosity of the liquid in centipoises, d is the specific gravity of the liquid tested at 20°/20°, and t is the time in seconds for the liquid to pass from the upper mark to the lower mark.

If a viscosimeter is repaired, it must be recalibrated, since even minor repairs frequently cause significant changes in the value of its constant, *k*.

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† Oils of known viscosities formerly supplied by the National Bureau of Standards, may be obtained from the Cannon Instrument Co., Post Office Box 16, State College, PA 16801. For methylcellulose, choose an oil the viscosity of which is as close as possible to that of the type of methylcellulose to be determined.

VITAMIN A ASSAY

Complete the assay promptly and exercise care throughout the procedure to avoid undue exposure to oxidizing agents, to actinic light, and to other conditions that destroy vitamin A. The use of nonactinic glassware is advantageous in avoiding destruction by light.

Isopropyl alcohol—Use *Isopropyl Alcohol*, distil, if necessary, to meet the following requirements for spectral purity: when measured in a 1-cm. cell against distilled water it shows an absorbance not greater than 0.05 at 300 mμ and not greater than 0.01 between 320 mμ and 350 mμ.

Ether—Use *Ether*, freshly distilled, discarding the first and last 10 percent portions, or *Ether*, anesthetic grade, from a freshly opened container.

Saponification—Transfer to a saponification flask an amount of the sample, accurately measured and expected to contain not less than the equivalent of 150 mcg. of vitamin A, but not more than 1 g. of fat. Reflux in an *all-glass* apparatus with 30 ml. of alcohol and 3 ml. of potassium hydroxide solution (1 in 2) for 30 minutes. Cool the solution, add 30 ml. of water, and transfer the resulting solution to a conical separator. Add 2 g. of finely powdered sodium sulfate. Extract, by shaking for 2 minutes, with one 150-ml. portion of ether, or, if an emulsion occurs, with three additional 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously until the last washing gives no color with phenolphthalein T.S. Transfer the washed ether extract to a 250-ml. volumetric flask, and dilute to volume with ether.

Procedure—Evaporate a 25.0-ml. aliquot of the ether solution of the unsaponifiable extract to about 5 ml. Without the application of heat, reduce the volume to about 3 ml. in a stream of inert gas or under reduced pressure. Dissolve the residue in sufficient isopropyl alcohol to give an expected concentration of the equivalent of 3 to 5 mcg. of vitamin A per ml. or such that it will give an absorbance in the range 0.4 to 0.8 at 325 mμ. Determine the absorbances of the resulting solution in 1-cm. cells, at 310 mμ, 325 mμ, and 334 mμ with a suitable spectrophotometer, using isopropyl alcohol as the blank.

Calculation—Calculate the vitamin A content as follows: Vitamin A content (in mg.) = $0.549 \times (A_{325}/LC)$, in which A_{325} is the observed absorbance at 325 mμ, L is the length, in cm., of the absorption cell, and C is the amount of sample expressed as g., capsule or tablet, in each 100 ml. of the final isopropyl alcohol solution, provided that A_{325} has a value not less than $A_{325}(\text{cor.})/1.030$ and not more than $A_{325}(\text{cor.})/0.970$, where $A_{325}(\text{cor.}) = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$, in which A designates the absorbance at the wavelengths indicated by the subscripts. Where A_{325} (cor.) has a value less than $A_{325}/1.030$ apply the following formula: Vitamin A content, in mg., = $0.549[A_{325(\text{cor.})}/LC]$. Each mg. of vitamin A (alcohol) represents 3333 USP Units of vitamin A.

Confidence Interval—The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P = 0.05$, is approximately ±8 percent.

VITAMIN B_{12} ACTIVITY ASSAY

Assay Preparation—Place a suitable quantity of the material to be assayed, accurately measured or weighed, in an appropriate vessel containing, for each g. or ml. of sample taken, 25 ml. of an aqueous extracting solution prepared just prior to use to contain, in each 100 ml., 1.29 g. of disodium phosphate, 1.1 g. of anhydrous citric acid, and 1.0 g. of sodium metabisulfite. Autoclave the mixture at 121° for 10 minutes. Allow any undissolved particles of the sample extract to settle, and filter or centrifuge if necessary. Dilute an aliquot of the clear solution with water so that the final test solution contains vitamin B_{12} activity approximately equivalent to that of the *Standard Cyanocobalamin Solution* which is added to the assay tubes.

Standard Cyanobalamin Stock Solution—To a suitable quantity of USP Cyanocobalamin Reference Standard, accurately weighed, add sufficient 25 percent alcohol to make a solution containing, in each ml., 1.0 mcg. of cyanocobalamin. Store in a refrigerator.

Standard Cyanocobalamin Solution—Dilute a suitable volume of *Standard Cyanocobalamin Stock Solution* with water to a measured volume such that after the incubation period as described under *Procedure*, the difference in transmittance between the inoculated blank and the 5.0-ml. level of the *Standard Cyanocobalamin Solution* is not less than that which corresponds to a difference of 1.25 mg. in dried cell weight. This concentration usually falls between 0.01 and 0.04 millimicrogram per ml. of *Standard Cyanocobalamin Solution*. Prepare a fresh standard solution for each assay.

Basal Medium Stock Solution—Add the ingredients in the order listed, carefully dissolving the cystine and tryptophane in the hydrochloric acid before adding the next eight solutions in the resulting solution. Add 100 ml. of water, mix, and dissolve the dextrose, sodium acetate, and ascorbic acid. Filter, if necessary, add the polysorbate 80 solution, adjust the reaction to pH 6.0 with 1 *N* sodium hydroxide, and add purified water to make 250 ml.

L-Cystine	0.1	g.
L-Tryptophane	0.05	g.
1 *N* Hydrochloric Acid	10	ml.
Adenine-Guanine-Uracil Solution	5	ml.
Xanthine Solution	5	ml.
Vitamin Solution I	10	ml.
Vitamin Solution II	10	ml.
Salt Solution A	5	ml.
Salt Solution B	5	ml.
Asparagine Solution	5	ml.
Acid-hydrolyzed Casein Solution	25	ml.
Dextrose, Anhydrous	10	g.
Sodium Acetate, Anhydrous	5	g.
Ascorbic Acid	1	g.
Polysorbate 80 Solution	5	ml.

Acid-hydrolyzed Casein Solution—Mix 100 g. of vitamin-free casein with 500 ml. of dilute hydrochloric acid (1 in 2), and reflux the mixture for 8 to 12 hours. Remove the hydrochloric acid from the mixture by distillation under reduced pressure until a thick paste remains. Redissolve the resulting paste in water, adjust the solution to a pH of 3.5 ± 0.1 with sodium hydroxide solution, and add water to make 1000 ml. Add 20 g. of activated charcoal, stir for 1 hour, and filter. Repeat the treatment with activated charcoal. Store under toluene in a refrigerator at a temperature not below 10°. Filter the solution if a precipitate forms under storage.

Asparagine Solution—Dissolve 2.0 g. of *l*-asparagine in water to make 200 ml. Store under toluene in a refrigerator.

Adenine-Guanine-Uracil Solution—Dissolve 200 mg. each of adenine sulfate, guanine hydrochloride, and uracil, with the aid of heat, in 10 ml. of dilute hydrochloric acid (1 in 3), cool, and add water to make 200 ml. Store under toluene in a refrigerator.

Xanthine Solution—Suspend 0.2 g. of xanthine in 30 to 40 ml. of water, heat to about 70°, add 6.0 ml. of ammonia T.S., and stir until the solid is dissolved. Cool, and add water to make 200 ml. Store under toluene in a refrigerator.

Salt Solution A—Dissolve 10 g. of monobasic potassium phosphate and 10 g. of dibasic potassium phosphate in water to make 200 ml. Add 2 drops of hydrochloric acid, and store under toluene.

Salt Solution B—Dissolve 4.0 g. of magnesium sulfate, 0.2 g. of sodium chloride, 0.2 g. of ferrous sulfate, and 0.2 g. of manganese sulfate in water to make 200 ml. Add 2 drops of hydrochloric acid, and store under toluene.

Polysorbate 80 Solution—Dissolve 20 g. of polysorbate 80 in sufficient alcohol to make 200 ml. Store in a refrigerator.

Vitamin Solution I—Dissolve 10 mg. of riboflavin, 10 mg. of thiamine hydrochloride, 0.1 mg. of biotin, and 20 mg. of nicotinic acid in sufficient 0.02 *N* acetic acid to make 400 ml. Store, protected from light, under toluene in a refrigerator.

Vitamin Solution II—Dissolve 20 mg. of para-aminobenzoic acid, 10 mg. of calcium pantothenate, 40 mg. of pyridoxine hydrochloride, 40 mg. of pyridoxal hydrochloride, 8 mg. of pyridoxamine dihydrochloride, and 2 mg. of folic acid in sufficient dilute neutralized alcohol (1 in 4) to make 400 ml. Store, protected from light, in a refrigerator.

Tomato Juice Preparation—Centrifuge commercially canned tomato juice so that most of the pulp is removed. Suspend about 5 g. per liter of analytical filter-aid in the supernatant liquid, and filter, with the aid of reduced pressure, through a layer of the filter-aid. Repeat if necessary until a clear, straw-colored filtrate is obtained. Store under toluene in a refrigerator.

Culture Medium—Dissolve 0.75 g. of water-soluble yeast extract, 0.75 g. of peptone, 1 g. of anhydrous dextrose, and 0.2 g. of potassium biphosphate in 60 to 70 ml. of water. Add 10 ml. of *Tomato Juice Preparation* and 1 ml. of *Polysorbate 80 Solution*. Adjust the solution to pH 6.8 with sodium hydroxide T.S., and add water to make 100 ml. Place 10-ml. portions of the solution in test tubes, and plug with cotton. Sterilize the tubes and contents in an autoclave at 121° for 15 minutes. Cool as rapidly as possible to avoid color formation resulting from overheating the medium.

Suspension Medium—Dilute a measured volume of *Basal Medium Stock Solution* with an equal volume of water. Place 10-ml. portions of the diluted medium in test tubes. Sterilize, and cool as directed above for the culture medium.

Stock Culture of the Lactobacillus leichmannii—To 100 ml. of culture medium add 1.0 to 1.5 g. of agar, and heat the mixture, with stirring, on a steam bath, until the agar dissolves. Place approximately 10-ml. portions of the hot solution in test tubes, cover the tubes suitably, sterilize at 121° for 15 minutes in an autoclave (exhaust line temperature), and allow the tubes to cool in an upright position. Inoculate three or more of the tubes, by stab transfer of a pure culture of *Lactobacillus leichmannii*.* (Before first using a fresh culture in this assay, make at least ten successive transfers of the culture in a two-week period.) Incubate 16 to 24 hours at any selected temperature between 30° and 40° but held constant to within ±0.5°, and finally store in a refrigerator.

Prepare fresh stab cultures at least three times each week, and do not use them for preparing the inoculum if more than 4 days old. The activity of the microorganism can be increased by daily or twice-daily transfer of the stab culture, to the point where definite turbidity in the liquid inoculum can be observed 2 to 4 hours after inoculation. A slow-growing culture seldom gives a suitable response curve, and may lead to erratic results.

Inoculum—Make a transfer of cells from the stock culture of *Lactobacillus leichmannii* to a sterile tube containing 10 ml. of the culture medium. Incubate this culture for 6 to 24 hours at any selected temperature between 30° and 40° but held constant to within ±0.5°. Under aseptic conditions, centrifuge the culture and decant the supernatant liquid. Suspend the cells from the culture in 10 ml. of sterile suspension medium. Dilute an aliquot with sterile suspension medium to give a transmittance that corresponds to a cell weight (as described under *Procedure*) of 0.5 mg. to 0.75 mg. per tube when read against the suspension medium set at 100 per cent transmittance.

Calibration of the Spectrophotometer—Add aseptically 1 ml. of *Inoculum* to approximately 300 ml. of suspension medium containing 0.5 ml. of *Standard Cyanocobalamin Stock Solution*. Incubate the inoculated medium for the same period and at the same temperature to be employed in the assay procedure.

Following the incubation period, centrifuge, and wash the cells three times with approximately 50-ml. portions of saline T.S., and then resuspend the cells in about 25 ml. of the saline solution.

Dry to constant weight a 10-ml. portion, accurately measured, using a steam bath and completing the drying under vacuum at 100°, and calculate the dry weight of the cells, in mg. per ml., corrected for the amount of sodium chloride present.

Dilute a second portion, accurately measured, of the saline cell suspension with the saline solution so that each ml. contains a known quantity of cells equivalent to 0.5 mg. on a dried basis. To test tubes add, in triplicate, 0.5 ml., 1.0 ml., 1.5 ml., 2.0 ml., 2.5 ml., 3.0 ml., 4.0 ml., and 5.0 ml., respectively, of this diluted cell suspension and 5.0 ml. of *Basal Medium Stock Solution*, and make up the volume in each tube to 10.0 ml. with saline solution. Using as the blanks three similar tubes containing no cell suspension, measure the light transmittance of each tube under the same conditions to be employed in the assay. Plot the observations as the ordinate on cross-section paper against the cell content, expressed as mg. of dry weight, as the abscissa.

Repeat the procedure at least twice for the spectrophotometer to be used in the assay. Draw the composite curve best representing the three or more individual curves relating transmittance to cell density for the spectrophotometer under the conditions of the assay.

Procedure—Cleanse meticulously by suitable means, followed preferably by heating at 250° for 2 hours, hard-glass test tubes, about 20 × 150 mm. in size, and other necessary glassware because of the high sensitivity of the test organism to minute amounts of vitamin B_{12} activity and to traces of many cleansing agents.

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* American Type Culture Collection No. 7830 is suitable.

To test tubes add, in duplicate, 1.0 ml. or 1.5 ml., 2.0 ml., 3.0 ml., 4.0 ml., and 5.0 ml., respectively, of the *Standard Cyanocobalamin Solution.* To each tube and to four similar tubes containing no *Standard Cyanocobalamin Solution* add 5.0 ml. of *Basal Medium Stock Solution* and sufficient water to make 10 ml.

To similar test tubes add, in duplicate, respectively, 1.0 ml. or 1.5 ml., 2.0 ml., 3.0 ml., and 4.0 ml., of the *Assay Preparation.* To each tube add 5.0 ml. of *Basal Medium Stock Solution* and sufficient water to make 10 ml. Place one complete set of Standard and Assay tubes together in one tube rack and the duplicate set in a second rack or section of a rack, preferably in random order.

Cover the tubes suitably to prevent bacterial contamination, and sterilize the tubes and contents in an autoclave at 121° for 5 minutes, arranging to reach this temperature in not more than 10 minutes by preheating the autoclave if necessary. Cool as rapidly as practicable to avoid color formation resulting from overheating the medium. Take precautions to maintain uniformity of sterilizing and cooling conditions throughout the assay, since packing tubes too closely in the autoclave, or overloading it, may cause variation in the heating rate.

Aseptically add 1 drop of *Inoculum* to each tube so prepared except two of the four containing no *Standard Cyanocobalamin Solution* (the uninoculated blanks). Incubate the tubes at a temperature between 30° and 40° held constant to within ±0.5°, until, following 16 to 24 hours of incubation, there has been no substantial increase in turbidity in the tubes containing the highest level of standard during a 2-hour period.

Determine the transmittance of the tubes in the following manner. Mix the contents of each tube, to which 1 drop of a suitable antifoam agent solution may be added, and transfer to an optical container. After agitating its contents, place the container in a spectrophotometer that has been set at a specific wavelength between 540 mμ and 660 mμ, and read the transmittance when a steady state is reached. This steady state is observed a few seconds after agitation when the reading remains constant for 30 seconds or more. Allow approximately the same time interval for the reading on each tube.

With the transmittance set at 1.00 for the uninoculated blank, read the transmittance of the inoculated blank. If this transmittance reading corresponds to a dried cell weight greater than 0.6 mg. per tube, or if there is evidence of contamination with a foreign microorganism, disregard the results of the assay.

Then with the transmittance set at 1.00 for the inoculated blank, read the transmittance for each of the remaining tubes. Disregard the results of the assay if the difference between the transmittance observed at the highest level of the standard and that of the inoculated blank is less than the difference corresponding to a dried cell weight of 1.25 mg. per tube.

Calculation—Prepare a standard concentration-response curve by the following procedure. Test for and replace any aberrant individual transmittances. For each level of the standard, calculate the response from the sum of the duplicate values of the transmittance as the difference, $y = 2.00 - \Sigma$ (of transmittance). Plot this response on the ordinate of cross-section paper against the logarithm of the ml. of *Standard Cyanocobalamin Solution* per tube on the abscissa, using for the ordinate either an arithmetic or a logarithmic scale, whichever gives the better approximation to a straight line. Draw the straight line or smooth curve which best fits the plotted points.

Calculate the response, y, adding together the two transmittances for each level of the *Assay Preparation.* Read from the standard curve the logarithm of the volume of the *Standard Preparation* corresponding to each of those values of y that fall within the range of the lowest and highest points plotted for the standard. Subtract from each logarithm so obtained the logarithm of the volume, in ml., of the *Assay Preparation* to obtain the difference, x, for each dosage level. Average the values of x for each of three or more dosage levels to obtain $\bar{x} = M'$, the log-relative potency of the *Assay Preparation.* Determine the quantity, in mcg., of USP Cyanocobalamin Reference Standard corresponding to the cyanocobalamin in the portion of material taken for assay as antilog M = antilog$(M' + \log R)$, where R is the number of mcg. of cyanocobalamin that was assumed to be present in each mg. (or capsule or tablet) of the material taken for assay.

Replication—Repeat the entire determination at least once, using separately prepared *Assay Preparations.* If the difference between the two log potencies M is not greater than 0.08, their mean, $\bar{M}$, is the assayed log-potency of the test material (see *Design and Analysis of Biological Assays*, USP XVIII). If the two determinations differ by more than 0.08, conduct one or more additional determinations. From the mean of two or more values of M that do not differ by more than 0.15, compute the mean potency of the preparation under assay.

VITAMIN D ASSAY

Biological Method

The biological assay of vitamin D comprises the recording and interpretation of observations on groups of rats maintained on specified dietary regimens throughout specified periods of their lives whereby the biological response to the preparation under assay is compared with the response to USP Vitamin D Reference Standard.

Preliminary Period—Throughout the preliminary period in the life of a rat, which is not longer than 30 days and extends from birth to the first day of the depletion period, maintain litters of rats under the immediate supervision of, or according to the directions of, the individual responsible for the assay. During the preliminary period, use a dietary regimen which provides for normal development but is limited in its content of vitamin D, so that when placed upon the *Rachitogenic Diet* in the depletion period the rats develop rickets. At the end of the preliminary period, reject any rat which weighs less than 44 g. or more than 60 g., or which shows evidence of injury, disease, or anatomical abnormality.

Depletion Period—Through the depletion period, which extends from the end of the preliminary period to the first day of the assay period, provide each rat *ad libitum* with the *Rachitogenic Diet* and water and allow access to no other food or dietary supplement.

Rachitogenic Diet—The rachitogenic diet consists of a uniform mixture of the following ingredients in the proportions shown:

	Parts by Weight
Whole Yellow Corn, ground	76
Ground Wheat Gluten	20
Calcium Carbonate	3
Sodium Chloride	1

When a chemical analysis of the entire ration shows a Ca:P ratio of less than 4:1 or more than 5:1, the proportion of calcium carbonate may be varied to bring the adjusted ratio to a uniform level within this range.

Assigning Rats to Groups for the Assay Period—Consider a litter suitable for the assay period when individual rats in the litter show evidence of rickets such as enlarged joints and a distinctive wobbly, rachitic gait, provided that the depletion period is not less than 19 or more than 25 days. The presence of rickets may be established also from the width of the rachitic metaphysis upon X-ray examination or by applying the line test (described below) to a leg bone of one member of each litter.

Record the weight of each rat and assign it to a group, in which each rat will be fed a specified dose of the reference standard or of an assay sample that is under examination for its vitamin D potency. For each assay sample provide one or more assay groups and at least two standard groups. The two standard groups may be used for the concurrent assay of more than one assay sample. Within an interval not exceeding 30 days, complete the assignment of rats to groups according to a design which divides litters among the groups, to achieve a complete balance.

For complete balance, whereby each litter is represented equally in every group, use seven or more litters containing at least as many depleted rats as there are groups. From a given litter, assign one rat, selected at random, to each group on the same day. If a litter contains twice as many rats as there are groups, assign a second series of rats similarly. The last one or two litters to be assigned may be allotted to groups so that at the start of the assay period the average body weight of any completed groups will not differ by more than 8 g. from that of any other group.

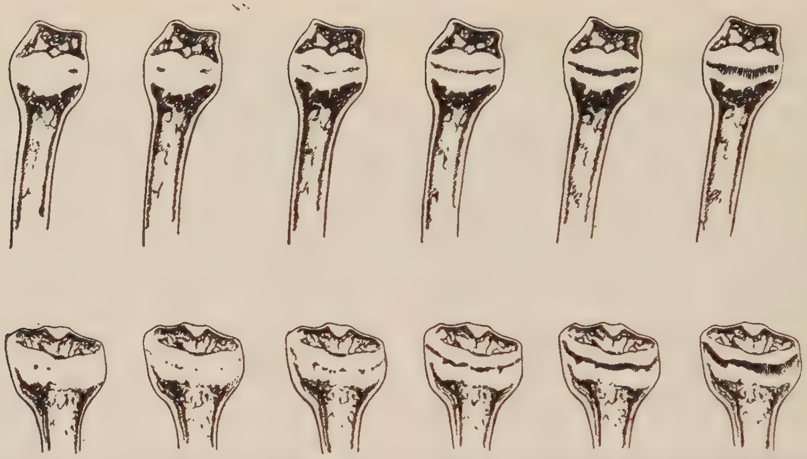
Assay Doses—Select two dosage levels of the USP Vitamin D Reference Standard, spaced so that the ratio of the larger to the smaller dose is not less than 1.5 or more than 2.5. Select one or two dosage levels based upon a single assumed potency for each sample. The dosage levels of the sample are equivalent to those of the standard or to a mid-level equal to the square root of the product of the two dosage levels of the standard.

Select dosage levels such that, when fed to rachitic rats, they are expected to produce degrees of calcification within the range specified under the test of data acceptability. Before feeding, the reference standard and/or sample may be diluted with cottonseed oil, provided that not more than 0.2 ml. is fed on any one day. Store the oil solutions in well-closed bottles, protected from light, at a temperature not exceeding 10°, and use within 5 weeks.

Assign one group of rats to each dosage level of the standard and of the one or more samples.

Assay Period—During the assay period, which extends from the end of the depletion period for a fixed interval of 7 to 10 days, cage each rat individually and provide it *ad libitum* with the *Rachitogenic Diet* and water. Supply a rachitogenic diet prepared from the same lots of ingredients to all rats. On the first and on the third (or fourth) day of the assay period, feed each rat one-half of its total assigned dose.

Throughout the assay period, maintain as uniform environmental conditions as possible for all rats and exclude exposure to



Representative Sections Showing the Radius (upper row) and the Tibia (lower row) in Graded Degrees of Healing in Rachitic Rats within the Useful Range of the Dosage-Response Relationship of the Vitamin D Assay

antirachitic radiations. At the end of a fixed period of 7 to 10 days, weigh and kill each rat. From those rats which do not weigh less at the end than at the start of the assay period and which have consumed each assigned dose within 24 hours of the time it was fed, dissect out one or more leg bones for examination by the *Line Test*.

Line Test—Remove the proximal end of a tibia or the distal end of a radius and clean it of adhering tissue, in any one assay using the same bone from all animals. With a clean, sharp blade cut a median, longitudinal section through the juncture of the epiphysis and diaphysis at the same place on each bone. Rinse both sections in purified water, immerse immediately in silver nitrate solution (1 in 50) for 1 minute, and rinse again in purified water. Expose the cut surface of bone, in water, to daylight or another source of actinic light until the calcified areas develop a clearly defined stain without marked discoloration of the uncalcified areas. The staining procedure may be modified to differentiate more clearly between calcified and uncalcified areas.

Score the degree of calcification of the rachitic metaphysis in each rat, according to a scale which allows the average response to be plotted as a straight line against the logarithm of the dose. The figure presented illustrates the range of the degree of calcification best suited for assay purposes.

Acceptability—Observations are acceptable for use in calculation of the potency only from those groups in which two-thirds or more but not less than 7 rats show calcification at least as great as the lowest level and not greater than the highest level illustrated in the figure. If the average score of the standard group on the high dosage level is not greater than the average score of the standard group on the low dosage level, discard the results and repeat the assay. If an assay sample is represented solely by assay groups which are not acceptable for measuring vitamin D potency and in each of which the average score is less than the average score of the standard group on the low dosage level or more than the average score of the standard group on the high dosage level, its assayed content of vitamin D is respectively less than that represented by the low dose or more than that represented by the high dose of the Reference Standard.

Calculation—Tabulate the scores (y), listing each litter in a separate row with treatment groups in columns. Omit any groups which do not meet the test for *Acceptability*. Equalize the number of observations in the acceptable groups by disregarding the results on all litters not equally represented in the groups or by other suitable means (see *Design and Analysis of Biological Assays*, USP XVIII). Total the f scores for each of the treatment groups, where f is the number of litters, and designate each total as T with subscripts 1 and 2 for the low and high dosage levels, respectively. Compute the slope b from the sums of T_1, *i.e.*, ΣT_1, and of T_2, *i.e.*, ΣT_2, for the standard and sample, provided the latter is represented at both dosage levels as $b = (\Sigma T_2 - \Sigma T_1)/ifh'$, where i is the logarithm of the ratio of the high dose to the low dose and is the same for each preparation, and h' is the number of preparations represented by two dosage levels and included in the calculation of the value of b.

Compute the logarithm of the relative potency of each sample under assay as log (relative potency) $= M' = (\bar{y}_U - \bar{y}_S)/b = ih'T_a/2\Sigma T_b$, where each mean score, $\bar{y}_U$ for the assay sample and $\bar{y}_S$ for the Reference

Standard, is the average of the individual scores for an intermediate dosage level or of the two means for the high and the low dosage levels and where $T_b = \Sigma T_2 - \Sigma T_1$ and T_a is defined in USP XVIII. Convert each observed M' to its antilogarithm to obtain the relative potency of the sample. Multiply the relative potency by the assumed potency of the assay oil in Units per g., adopted at the start of the assay, to obtain its assayed content of vitamin D in USP Units per g.

Chemical Method

The following procedure is provided for the determination of vitamin D as an ingredient of official preparations containing other active constituents.

Special Reagents and Solutions—

Chromatographic Fuller's Earth—Use chromatographic fuller's earth having a water content corresponding to not less than 8.5 percent and not more than 9.0 percent of loss on drying.

Solvent Hexane—Use reagent solvent hexane (see USP XVIII), distilling if necessary so that it meets the following additional specification:

Spectral purity—Measure in a 1-cm. cell at 300 mμ, with a suitable spectrophotometer, against air as the blank: the absorbance is not more than 0.070.

Ethylene Dichloride—Purify by passage through a column of granular (20 to 200 mesh) silica gel.

Potassium Hydroxide Solution—Dissolve 780 g. of potassium hydroxide in water to make 1000 ml.

Cottonseed Oil—Use cottonseed oil USP that meets the following additional requirement: Saponify 10 g. of the oil as directed in this chapter under *Sample Preparation*, beginning with "then add a volume of *Potassium Hydroxide Solution*," and dissolve the unsaponifiable residue in 10 ml. of *Solvent Hexane*.

In a separate container place 0.4 ml. of ferric chloride solution (1 in 1000) and 12 ml. of a 1 in 6000 solution of 2,2′-bipyridine in dehydrated alcohol, mix, and 5 minutes later read the absorbance in a 1-cm. cell at 520 mμ, with a suitable spectrophotometer, using dehydrated alcohol as the blank. Then add 0.2 ml. of the solvent hexane solution of the unsaponifiable residue, and after 5 minutes read the absorbance. The difference between the first and the second absorbances is not less than 0.125.

Color Reagent—Prepare two stock solutions as follows.

Solution A—Empty, without weighing, the entire contents of a previously unopened 113-g. bottle of dry, crystalline antimony trichloride into a flask containing about 400 ml. of *Ethylene Dichloride*. Add about 2 g. of anhydrous alumina, mix, and filter through filter paper into a clear-glass, glass-stoppered, container calibrated at 500 ml. Add *Ethylene Dichloride* to make 500 ml., and mix: the absorbance of the solution, measured in a 2-cm. cell at 500 mμ, with a suitable spectrophotometer, against *Ethylene Dichloride*, does not exceed 0.070.

Solution B—Mix, under a hood, 100 ml. of acetyl chloride and 400 ml. of *Ethylene Dichloride*.

Mix 45 ml. of *Solution A* and 5 ml. of *Solution B* to obtain the *Color Reagent*. Store in a tight container, and use within 7 days, but discard any reagent in which a color develops.

Chromatographic Tubes—

First Column—Arrange for descending column chromatography (see page 786) a tube of 2.5 cm. (inside) diameter, about 25 cm. long, and constricted to 8 mm. diameter for a distance of 5 cm. at the lower end, by inserting at the point of constriction a coarse-porosity, sintered-glass disk or a small plug of glass wool. The constricted portion may be fitted with an inert, plastic stopcock.

Second Column—Select a tube that is made up of three sections: (1) a flared top section, 18 mm. in (inside) diameter and approximately 14 cm. long, (2) a middle section, 6 mm. in (inside) diameter and approximately 25 cm. long, and (3) a tapered, constricted lower exit tube approximately 5 cm. long. Insert a small plug of glass wool in the upper 1-cm. portion of the constricted section.

Chromatographic Columns—

First Column—To about 125 ml. of isooctane contained in a screw-cap, wide-mouth bottle add 25 g. of chromatographic siliceous earth, and shake until a slurry is formed. Add, dropwise and with vigorous mixing, 10 ml. of polyethylene glycol 600. Replace the bottle cover, and shake vigorously for 2 minutes. Pour about half of the resulting slurry into the chromatographic tube, and allow it to settle by gravity. Then apply gentle suction, and add the remainder of the slurry in small portions, packing each portion with a 20-mm. disk plunger. When a solid surface has formed, remove the vacuum, and add about 2 ml. of isooctane.

Second Column—Pack the midsection of the tube with 3 g. of moderately coarse *Chromatographic Fuller's Earth* with the aid of gentle suction (about −125 mm. of mercury).

Standard Preparation—Dissolve about 25 mg. of USP Ergocalciferol Reference Standard, accurately weighed, in sufficient isooctane to make 100.0 ml. Store in a refrigerator.

On the day of assay, pipet 1.0 ml. of the standard solution into a 50-ml. volumetric flask, remove the solvent with a stream of nitrogen, and dissolve the residue in, and dilute to volume with, *Ethylene Dichloride*.

Sample Preparation—Unless otherwise

directed, accurately weigh or measure a portion of the sample to be assayed, equivalent to not less than 125 mcg. but preferably about 250 mcg. of ergocalciferol (10,000 USP Units). If little or no vitamin A is present in the sample, add about 1.5 mg. (the equivalent of 5000 USP Units) of vitamin A to provide the needed pilot bands in the subsequent chromatography.

For capsules or tablets, reflux not less than 10 of them in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for 5 minutes longer.

Add 2 ml. of *Cottonseed Oil,* then add a volume of *Potassium Hydroxide Solution* representing 2.5 ml. for each g. of the total weight of the sample plus cottonseed oil, but not less than 15 ml. Add 50 ml. of alcohol. Reflux vigorously on a steam bath for 20 minutes, or for 30 minutes for samples weighing more than 5 g. If oil globules are evident, indicating incomplete saponification, add 5 ml. of *Potassium Hydroxide Solution* (but not exceeding a total of 100 ml.), and heat again. Cool, and transfer the saponified mixture to a 500-ml. separator, rinsing the saponification flask with a total of 50 ml. of water and adding each rinse to the separator. Add about 4.5 g. of sodium sulfate decahydrate and 150 ml. of *Solvent Hexane.* Shake vigorously for 2 minutes. When the aqueous layer has separated, transfer it to a second separator. Extract with two 50-ml. portions of *Solvent Hexane,* combine the extracts, and discard the aqueous solution.

Wash the combined solvent hexane extracts with 50-ml. portions of water until the last portion shows no pink color on the addition of phenolphthalein T.S. Allow the washed extract to stand for 5 minutes, discard any water that separates, and transfer the extract to a 300-ml. tall form beaker containing about 5 g. of anhydrous sodium sulfate. Stir for 2 minutes, and decant the solution into a 500-ml., tall-form beaker. Rinse the sodium sulfate with four 25-ml. portions of *Solvent Hexane,* combining the rinsings with the original extract. Reduce the total volume to about 30 ml. by evaporation on a steam bath, and transfer the concentrate to a small, round-bottom evaporation flask. Rinse the beaker with four 5-ml. portions of *Solvent Hexane,* adding the rinsings to the flask. With the aid of vacuum in a water bath at a temperature not exceeding 40°, or with a stream of nitrogen at room temperature, remove the remaining solvent completely. Dissolve the residue in a small amount of *Solvent Hexane,* transfer to a 10-ml. volumetric flask, and dilute with *Solvent Hexane* to volume to obtain the *Sample Preparation.*

Procedure—

First Column Chromatography—Just as the 2 ml. of isooctane disappears into the surface of the prepared *First Column,* pipet 2.0 ml. of the *Sample Preparation* onto the column. As the meniscus of the *Sample Preparation* reaches the column surface, add the first of three 2-ml. portions of *Solvent Hexane,* adding each succeeding portion as the preceding portion disappears into the column. Continue adding *Solvent Hexane* in portions of 5 to 10 ml. until 100 ml. has been added. If necessary, adjust the flow rate to between 3 and 6 ml. per minute, by application of gentle pressure at the top of the chromatographic tube.

Discard the first 20 ml. of effluent, and collect the remainder. Examine the column under ultraviolet light at intervals during the chromatography, and stop the flow when the front of the fluorescent band representing vitamin A is about 5 mm. from the bottom of the column. (The ultraviolet lamp should provide *weak* radiation in the 300-mμ region. It is frequently necessary to use a narrow aperture or screen with commercial lamps to reduce the amount of radiation to the minimum required to visualize the vitamin A on the column.)

Transfer the eluate to a suitable evaporation flask, and remove the solvent hexane completely under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature. Dissolve the residue in about 10 ml. of *Solvent Hexane.*

Second Column Chromatography—Add the solvent hexane solution obtained as directed under *First Column Chromatography* onto the *Second Column.* Rinse the evaporation flask with a total of 10 ml. of solvent hexane in small portions, adding each portion to the *Second Column* and allowing it to flow through the column, and discard the effluent. When about 1 ml. of the solvent hexane remains above the surface of the column, add 75 ml. of benzene, and elute with the aid of gentle suction (about 125 mm. of mercury), collecting the eluate. Evaporate the benzene under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature.

Assay Preparation—Dissolve the residue obtained as directed under *Second Column Chromatography* in a small amount of *Ethylene Dichloride,* transfer to a 10-ml. volumetric flask, and dilute to volume with *Ethylene Dichloride* to obtain the *Assay Preparation.*

Color Development—Into each of three suitable, matched colorimeter tubes of about 2-cm. diameter, and designated *1,* *2,* and *3,* respectively, pipet 1.0 ml. of the *Assay Preparation.* Into tube *1* pipet 1.0 ml. of the *Standard Preparation,* into tube *2,* 1.0 ml. of *Ethylene Dichloride,* and into tube *3,* 1.0 ml. of a mixture of equal volumes of acetic anhydride and *Ethylene Dichloride.* To each tube add quickly, and preferably from an automatic pipet, 5.0

ml. of *Color Reagent*, and mix. Exactly 45 seconds after the addition of the color reagent, determine the absorbances of the three solutions at 500 mμ, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank. Similarly, 45 seconds after making the first reading on each solution, determine the absorbances of the solutions in tubes *2* and *3* at 550 mμ, in a similar manner. Designate the absorbances as A^1_{500}, A^2_{500}, A^3_{500}, A^2_{550}, and A^3_{550}, respectively, in which the superscript indicates the number of the tube and the subscript the wavelength.

Calculation—Calculate the quantity, in mcg., of vitamin D in the portion of the sample taken by the formula $(C_S/C) \times (A_U/A_S)$, in which C_S is the concentration of vitamin D in mcg. per ml. of the *Standard Preparation*, C is the concentration of the sample (as g., capsules, tablets, etc.) in each ml. of the final solution, A_U has the value of $(A^2_{500} - A^3_{500}) - 0.67(A^2_{550} - A^3_{550})$ determined from the absorbances observed on the solution from the *Assay Preparation*, and A_S has the value of $A^1_{500} - A^2_{500}$ determined on the solution from the *Standard Preparation*.

VOLUMETRIC APPARATUS

Most of the volumetric apparatus available in the United States is calibrated at 20°, although the temperatures generally prevailing in laboratories more nearly approach 25°, which is the temperature specified generally for National Formulary tests and assays. This discrepancy is inconsequential provided the room temperature is reasonably constant and the apparatus has been calibrated accurately prior to and under the conditions of its intended use.

Use—To attain the degree of precision required in many NF assays involving volumetric measurements and directing that a quantity be "accurately measured," the apparatus must be chosen and used with exceptional care. Where less than 10 ml. of titrant is to be measured, a 10-ml. buret or microburet generally is required.

The design of volumetric apparatus is an important factor in assuring accuracy. For example, the length of the graduated portions of graduated cylinders should be not less than five times the inside diameter, and the tips of burets should permit an outflow rate of not more than 0.5 ml. per second.

Standards of Accuracy—The capacity tolerances for volumetric flasks, transfer pipets, and burets are those accepted by the National Bureau of Standards,* as indicated in the accompanying tables.

The capacity tolerances for measuring (*i.e.*, "graduated") pipets of up to and including 10-ml. capacity are somewhat larger than those for the corresponding sizes of transfer pipets, namely, 10, 20, and 30 μl. for the 2, 5, and 10-ml. sizes, respectively.

Transfer and measuring pipets calibrated "to deliver" should be drained in a vertical position and then touched against the wall of the receiving vessel to drain the tips. Volume readings on burets should be estimated to the nearest 10 μl. for 25 and 50-ml. burets, and to the nearest 5 μl. for 5 and 10-ml. burets. Pipets calibrated "to contain" are called for in special cases, generally for measuring viscous fluids like syrups. In such cases, the pipet should be washed clean, after draining, and the washing added to the measured portion.

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* See "Testing of Glass Volumetric Apparatus," NBS Circ. 602, April 1, 1959.

Volumetric Flasks

Designated volume, ml.	10	25	50	100	250	500	1000
Limit of error, ml.	0.02	0.03	0.05	0.08	0.12	0.15	0.30
Limit of error, percent	0.20	0.12	0.10	0.08	0.05	0.03	0.03

Transfer Pipets

Designated volume, ml.	1	2	5	10	25	50	100
Limit of error, ml.	0.006	0.006	0.01	0.02	0.03	0.05	0.08
Limit of error, percent	0.60	0.30	0.20	0.20	0.12	0.10	0.08

Burets

Designated volume, ml.	10 ("micro" type)	25	50
Subdivisions, ml.	0.02	0.10	0.10
Limit of error, ml.	0.02	0.03	0.05

WATER DETERMINATION

Titrimetric Method

Principle—The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulfur dioxide and iodine dissolved in pyridine and methanol. The sample may be titrated with the *Reagent* directly, or the analysis may be carried out by a residual titration procedure. In the residual titration, excess *Reagent* is added to the sample, sufficient time is allowed for the reaction to reach completion, and the unconsumed *Reagent* is titrated with a standard solution of water in methanol. The residual titration procedure is applicable generally and avoids the difficulties which may be encountered in the direct titration of substances from which the bound water is released slowly.

The stoichiometry of the reaction is not exact and the reproducibility of a determination depends upon such factors as the relative concentrations of the *Reagent* ingredients, the nature of the inert solvent used to dissolve the sample, and the technique used in the particular determination. Therefore, an empirically standardized technique must be used in order to achieve the desired accuracy. Precision in the method is governed largely by the extent to which atmospheric moisture is excluded from the system.

Apparatus and End-Point Determination—In the case of a colorless solution which is titrated directly, the end-point may be observed visually as a change in color from canary yellow to amber. The reverse is observed in the case of a sample which is titrated residually. More commonly, however, the end-point is determined electrometrically by the dead-stop titration method with use of dual platinum electrodes and a polarizing current of about 5 to 10 microamperes. When completion of the reaction is reached, a change in the electrochemical properties of the solution is sensed by the electrodes and the end-point is indicated by the deflection of a microammeter or by means of some other current-sensing device or a potential sensing device. With some automatic titrators, the abrupt change in current at the end-point serves to close a solenoid-operated valve which controls the buret delivering the titrant. Commercially available apparatus generally comprises a closed system consisting of one or two automatic burets and a tightly covered titration vessel fitted with the appropriate electrodes and a magnetic stirrer. The air in the system is kept dry with a suitable desiccant such as phosphorus pentoxide, anhydrous granular calcium chloride, or silica gel, and the titration vessel may be purged by means of a stream of dry nitrogen.

Reagent—The *Reagent* (*Karl Fischer*) may be obtained commercially as a stabilized solution or may be prepared as follows: Add 125 g. of iodine to a solution containing 670 ml. of methanol and 170 ml. of pyridine, and cool. Place 100 ml. of pyridine in a 250-ml. graduated cylinder and, keeping the pyridine cold in an ice bath, pass in dry sulfur dioxide until the volume reaches 200 ml. Slowly add this solution, with shaking, to the cooled iodine mixture. Shake well to dissolve the iodine, transfer the solution to the apparatus, and allow to stand overnight before standardizing. One ml. of this *Reagent*, when freshly prepared, is equivalent to approximately 5 mg. of water. For prolonged storage in bulk, preserve the *Reagent* in sealed, glass-stoppered, light-resistant containers, preferably in a refrigerator.

Standardization of the Reagent—The *Reagent* is subject to gradual deterioration and should be standardized on each day of use by either of the following methods:

Primary Standardization—Transfer 35 to 40 ml. of methanol to the titration vessel and titrate with the *Reagent* to the end-point to consume any moisture which may be present. Quickly add 150 to 350 mg. of sodium tartrate ($Na_2C_4H_4O_6.2H_2O$), accurately weighed by difference, and again titrate to the end-point with the *Reagent*. Calculate the water equivalence factor F, in mg. of water per ml. of *Reagent*, by the formula $0.1566\ W/V$, where W is the weight, in mg., of sodium tartrate, and V is the volume, in ml., of the *Reagent* consumed in the second titration.

Secondary Standardization—Prepare a *Water-Methanol Solution* by diluting 2 ml. of water to 1000 ml. with methanol. Standardize this solution by titrating 25.0 ml. with the *Reagent*, previously standardized as directed under *Primary Standardization*. Calculate the water content, in mg. per ml., of the *Water-Methanol* solution by the formula $V'F/25$, in which V' is the volume of the *Reagent* consumed, and F is the water equivalence factor of the *Reagent*. The water content of the *Water-Methanol Solution* should be determined weekly and the *Reagent* standardized against it periodically as needed.

Procedure—Water shall be determined by the *Direct Titration* procedure unless otherwise stated in the individual monograph.

Direct Titration—Unless otherwise specified, transfer 35 to 40 ml. of methanol to the titration vessel, and titrate with the *Reagent* to the electrometric end-point to consume any moisture which may be present. Quickly add an accurately weighed or measured amount of the sample estimated to contain 10 to 50 mg. of water, mix, and again titrate with the *Reagent* to the electrometric end-point. Calculate the water content of the sample, in mg., by the formula $S \times F$, in which S is the volume, in ml., of the *Reagent* consumed in the second titration, and F is the water equivalence factor of the *Reagent*.

Residual Titration—If an individual monograph specifies that the water content be determined by the *Residual Titration* procedure, transfer 35 to 40 ml. of methanol to the titration vessel, and titrate with the *Reagent* to the electrometric end-point. Quickly add an accurately weighed or measured amount of the sample estimated to contain 10 to 50 mg. of water, mix, and add an accurately measured excess of the *Reagent*. Allow sufficient time for the reaction to reach completion, and then titrate the unconsumed *Reagent* with standardized *Water-Methanol Solution* to the electrometric end-point. Calculate the water content of the sample, in mg., by the formula $F \times (X' - XR)$, in which F is the water equivalence factor of the *Reagent;* X' is the volume, in ml., of the *Reagent* added after introduction of the sample; X is the volume, in ml., of standardized *Water-Methanol Solution* required to neutralize the unconsumed *Reagent;* and R is the ratio, $V'/25$ (ml. *Reagent*/ml. *Water-Methanol Solution*), determined from the *Secondary Standardization*.

WEIGHT VARIATION

Capsules

Capsules meet the requirements of the following test with respect to variation in weight.

Hard Capsules—Weigh 20 intact capsules individually and determine the average weight. The sample meets the requirements if each of the individual weights falls within the limits of 90 percent and 110 percent of the average weight.

If not all of the capsules fall within the aforementioned limits, weigh the 20 capsules individually, taking care to preserve the identity of each capsule, and remove the contents of each capsule with the aid of a small brush or pledget of cotton. Weigh the emptied shells individually and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. Determine the average net weight from the sum of the individual net weights. Determine the difference between each individual net weight and the average net weight: the sample meets the requirements if (a) not more than two of the differences are greater than 10 percent and (b) in no case is the difference greater than 25 percent.

If more than 2 but less than 7 capsules deviate from the average between 10 percent and 25 percent, determine the net contents of an additional 40 capsules, and determine the average content of the entire 60 capsules. Determine the 60 deviations from the new average: the sample meets the requirements if in not more than 6 of the entire 60 capsules does the difference exceed 10 percent of the average, and in no case does the difference exceed 25 percent.

Soft Capsules—Soft capsules conform to the tolerances provided for *Hard Capsules*. Proceed as directed under *Hard Capsules*, except determine the net weight of the contents of individual capsules as follows: Weigh the intact capsules individually to obtain their gross weights, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells and calculate the net weight of the contents.

Creams, Ointments, and Powders

The following tests and specifications apply to fill tolerances for creams, ointments, and powders when packaged in nonunit dosage containers in which the labeled net weight is not more than 150 g.

Select a sample of 10 filled containers and remove any paper labels. Thoroughly cleanse and dry the outside of the containers by a suitable means, removing any labeling which might be altered in weight during the removal of the container contents, and weigh individually. Quantitatively remove the contents from each container, cutting them open and washing with a suitable solvent when necessary, being careful to retain any cutting or closure part with its proper container. Dry, and reweigh each empty container together with its corresponding cuttings and closure parts. The difference between the two weights is the net weight of the contents of the container. The average net weight of the contents of the 10 containers is not less than the labeled amount, and the net weight of the contents of any single container is not less than 90 percent of the labeled amount where the labeled amount is 60 g. or less, and not less than 95 percent of the labeled amount where the labeled amount is more than 60 g. but not more than 150 g.

If this requirement is not met, determine the net weight of the contents of 20 additional representative containers as described for the original 10 containers. The average net weight of the contents of 30 containers is not less than the labeled amount, and the net weight of the contents of not more than one of the 30 containers is less than 90 percent of the labeled amount where the labeled amount is 60 g. or less, and not less than 95 percent of the labeled amount where the labeled amount is more than 60 g. but not more than 150 g.

Sterile Solids

The following tests and specifications apply to fill tolerances of sterile solids packaged as dosage forms, with or without added substances. These sterile solids are supplied in suitable containers and are intended for parenteral use when suitably dissolved or suspended.

Select a sample of 20 filled containers. Cleanse and dry thoroughly, after removing any paper labels. Carefully open each container, and quickly weigh the container and its contents. Remove the latter by gentle tapping followed by rinsing with water and with alcohol. Dry the emptied container at 105° for 1 hour (or at a lower temperature to constant weight if the nature of the container precludes heating at 105°), cool in a desiccator, and weigh: the weight of the contents is the difference between the two weights. Calculate the average net weight of the contents of the 20 containers: the sample meets the requirements if (a) not more than 2 of the net weights of the 20 individual containers deviate by more than 10 percent from the average net weight, and (b) in no case does the net weight of an individual container deviate by more than 15 percent from the average net weight.

If this requirement is not met, select and determine the weight of the contents of 40 additional filled containers, as described for the original 20 containers. Calculate the average net weight of the contents of the 60 containers: the sample meets the requirement if (a) not more than 6 of the net weights of the 60 individual containers deviate by more than 10 percent from the average net weight, and (b) not more than 1 of the net weights of the 60 individual containers deviates by more than 15 percent from the average net weight.

Tablets

The average weight of uncoated tablets conforms to the tolerances given below unless otherwise provided in the individual monograph.

Weigh individually 20 whole tablets, and calculate the average weight: the weights of not more than 2 of the tablets differ from the average weight by more than the percentage listed and no tablet differs by more than double that percentage.

Tablets

Average Weight, mg.	Percentage Difference
130 or less	10
From 130 through 324	7.5
More than 324	5

WEIGHTS AND BALANCES

Official tests and assays are designed for use with three types of analytical balances known as macro-, semimicro-, and microbalances.

Tolerances—The analytical weights meet the tolerances of the National Bureau of Standards for class S if used without corrections, or meet the use tolerances for class S-1 if used with corrections. Where quantities of 25 mg. or less are to be "weighed accurately," any applicable corrections for weights should be used.

Use—Where substances are to be "accurately weighed" in an assay or a test, the weighing is to be performed in such manner as to limit the error to 0.1 percent or less. The proportionate accuracy should be the same whether 5 mg. or 100 mg. of a substance is weighed. For example, a quantity of 5 mg. is to be weighed to the nearest 5 mcg.; a quantity of 100 mg. is to be weighed to the nearest 100 mcg.; and a quantity of 10 g. is to be weighed to the nearest 10 mg.

X-RAY DIFFRACTION

X-ray diffraction is used for the identification of crystalline substances. Basically, the procedure consists of passing an essentially monochromatic beam of X-rays through a crystalline substance and observing the angular dispersion and intensity of the diffracted radiation. While studies in theoretical physics and crystal structure determination are usually carried out on single crystals of a substance, identification work is usually done with a powdered sample of the crystals, in which case the technique is called X-ray powder diffraction.

X-ray diffraction has the singular advantage over other identification techniques in that the sample is examined as presented (aside from a possible reduction in particle size). There is no need to dissolve the sample or to react it with reagents. The effect of impurities varies with the type of impurity involved; however, simple admixtures of different kinds of crystals are revealed as a superposition of the different X-ray patterns which would be produced by each of the types of crystals if they were pure. However, relatively small amounts of impurities, intimately distributed within the crystalline material, generally are not detected by X-ray diffraction, and therefore usually cause no interference.

Definitions—

Crystal—A solid material, the atoms and molecules of which are packed together in a regular three-dimensional pattern. Particle size is not a factor in the definition of a crystal. Crystals may be large and visible to the eye or as small as the particles of an impalpable powder. Also, birefringence or the lack of it is not a factor in the definition of the term. Many crystals are not birefringent, but some noncrystalline substances are birefringent. Furthermore, external shape is not a factor in the definition of the term, since a crystal may have no recognizable external shape. On the other hand, crystals that have lost crystallinity, as in drying, may retain their original external form. The crystals of some substances exhibit the phenomenon of polymorphism.

Polymorphism—The phenomenon by which the molecules of a given substance pack together in two or more satisfactory ways. Usually one polymorph, or phase, is more stable than another at a given temperature. Since polymorphism is a phenomenon of the solid state, only those techniques which treat a sample in the solid state can be used to study the condition. The X-ray patterns of polymorphs are as different as though two separate chemical entities were involved. While other analytical techniques which measure energy differences between polymorphs can be used to detect and study the condition, X-ray diffraction operates directly on atomic positions in crystals and thus detects polymorphism directly.

Interplanar Spacing [Symbol: *d*]—The distance between parallel planes in which the atoms of the crystal lie. The spacing between these planes in the three-dimensional lattice can be determined by X-ray diffraction. The dimensions of these spacings are usually given in terms of Angstroms (Å). The diffracted radiation from a crystal behaves as though it is reflected from these crystal planes; the term "reflection" is often used, although the actual process is diffraction.

X-Rays—Electromagnetic radiations at the short wavelength end of the electromagnetic spectrum. The output of an X-ray tube consists of a "white" background radiation plus a characteristic radiation, the wavelength of which is dependent on the element of which the target of the X-ray tube is made. This characteristic radiation can be rendered almost monochromatic by the use of suitable filters.

Theory—Since the distance between atoms in a crystal is of the same order of magnitude as the wavelength of an X-ray beam, a crystal can act as a diffraction grating for X-rays. If a single crystal is irradiated with an X-ray beam, the resulting diffraction pattern may be detected as an array of spots on a photographic film. Each spot will be the result of diffraction from a given set of planes of atoms in the crystal. The angle of the diffracted beam, with reference to the incoming primary X-ray beam, is given by the Bragg equation:

$$n\lambda = 2d \sin \theta,$$

in which n is the order of diffraction; λ is the wavelength of the X-ray, in Angstroms; d is the interplanar spacing in the crystal, in Angstroms; and θ is one-half of the angle between the primary beam projection and the diffracted beam.

If a powdered sample of crystals with random orientation is used, each crystallite will produce its own pattern, and the loci of the diffracted beams form a series of cones whose apexes, located at the sample, will be twice the angle between the primary beam projection and the diffracted beam. If these cones of radiation are intercepted and registered on a flat photographic film, a series of circles will result. The diameter of these circles can be measured, and the interplanar spacing can be calculated using the Bragg equation and the film-to-sample distance. Because of the nature of the diffraction process, each atom of the crystal contributes to each diffraction maximum of the finished pattern.

Apparatus—Two general types of apparatus are available, based upon whether the radiation will be received by film or by counter tube. The film technique usually requires less sample than the counter technique but is slower in total time from submission of sample to read-out of results. Both techniques give the same information.

Procedure—[*CAUTION: X-ray equipment should be used only by qualified personnel, in accordance with the manufacturer's instructions. The energy of the X-ray beam used in crystallographic study is quite different from that used in medical treatment. Improper use of the instrument can result in severe radiation damage.*]

Certain considerations apply to both film and counter techniques. The crystals must be in a powder form in order to help provide the random orientation that the method requires. If the crystals contain elements having a high X-ray absorption coefficient, such as barium or iodine, the sample should be diluted with a material such as starch or gum tragacanth. The X-rays may be generated with X-ray tubes of different types. The tubes should be equipped with proper filters so as to produce monochromatic radiation. (The most common system is a copper target X-ray tube with a nickel filter. However, if samples containing iron are to be examined, it is advantageous to use a tube with an iron target and a manganese filter.) The proper voltage and tube current are dependent on the target used, and the manufacturer's recommendations should be followed. The X-ray beam from the tube is passed through a collimator of proper shape and size and then is diffracted by the sample. An efficient beam stop should be provided, both for protection of the operator and to prevent background effects of scattered radiation.

In the film technique, the sample is placed in a capillary tube having an approximate inside diameter of 0.5 mm. The capillaries are made of noncrystalline materials having a low X-ray absorption coefficient, such as glass, or a plastic such as collodion. The capillary is then mounted on a rotating spindle and centered in the camera. (The sample rotation aids in providing random orientation.) The exposure time required is a function of the nature of the sample, the X-ray intensity, and film sensitivity.

In the counter technique, the sample is packed into a flat holder, making an effort to avoid preferred orientation. The holder is then inserted into one X-ray spectrometer in such a fashion that the X-rays will be diffracted from the flat surface of the sample into a counter tube, such as a Geiger-Müller tube. The output pulses of the counter tube are passed through a ratemeter, and the pattern appears as a recording on a strip-chart recorder. Intensity relationships of a given X-ray maximum with others of the same pattern may change when the method is changed from the film to the counter technique. This is caused by the change in the orientation of the crystals as presented to the X-ray beam. This change is most prominent when flat, plate-like crystals are examined.

The intensities of the X-ray maxima are presented as a ratio of I/I_1, in which I is the intensity of the maximum corresponding to the indicated d value, and I_1 is the intensity of the strongest maximum of the pattern.* Intensities may be read directly from a strip-chart recording, or, in the case of films, by comparison with a calibrated scale. In powder diffraction work, intensity data are intended only as a guide to strong and weak X-ray maxima. They may vary from laboratory to laboratory by as much as about 25 percent.

The errors in published data for interplanar spacings (d values) vary according to the size of the spacing. The error in d is inversely proportional to θ, as indicated by the Bragg equation. Variation of the observed d values from those given in the monograph are permissible up to a magnitude equivalent to $\pm 0.3° \theta$ (for a copper target X-ray tube).

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* Intensity ratio values (I/I_1) in individual monographs are based upon 100 for the strongest line. This is in accord with current ASTM practice. A lower case b following the value for I/I_1 in an individual monograph indicates a broad line resulting from failure to resolve two closely spaced diffraction maxima.

APPENDIX

CHROMIC ACID CLEANSING MIXTURE

Sodium Dichromate	200 g.
Water	100 ml.
Sulfuric Acid	1500 ml.

Dissolve the sodium dichromate in the water, then slowly and cautiously add the sulfuric acid with stirring.

pH VALUES OF BUFFER SOLUTIONS FOR STANDARDIZATION FROM 10° TO 60° C.

Temperature, °C.	Potassium Tetraoxalate 0.05 *M*	Potassium Biphthalate 0.05 *M*	Equimolar Phosphate 0.05 *M*	Sodium Tetraborate 0.01 *M*	Calcium Hydroxide, Saturated
10	1.67	4.00	6.92	9.33	13.00
15	1.67	4.00	6.90	9.28	12.81
20	1.68	4.00	6.88	9.23	12.63
25	1.68	4.01	6.86	9.18	12.45
30	1.68	4.02	6.85	9.14	12.29
35	1.69	4.02	6.84	9.10	12.13
40	1.69	4.04	6.84	9.07	11.98
45	1.70	4.05	6.83	9.04	11.84
50	1.71	4.06	6.83	9.01	11.71
55	1.72	4.08	6.83	8.99	11.57
60	1.72	4.09	6.84	8.96	11.45

SYSTEMS FOR NONAQUEOUS TITRATIONS

Type of Solvent	*Acidic* (for titration of bases and their salts)	*Relatively Neutral* (for differential titration of bases)	*Basic* (for titration of acids)	*Relatively Neutral* (for differential titration of acids)
Solvent[a]	Glacial Acetic Acid Acetic Anhydride Formic Acid Propionic Acid Sulfonyl Chloride	Acetonitrile Alcohols Chloroform Benzene Chlorobenzene Ethyl Acetate Dioxane	Dimethylformamide *n*-Butylamine Pyridine Ethylenediamine Morpholine	Acetone Acetonitrile Methyl Ethyl Ketone Methyl Isobutyl Ketone *tert*-Butyl Alcohol
Indicator	Crystal Violet Quinaldine Red *p*-Naphtholbenzein Alphazurine 2-G Malachite Green	Methyl Red Methyl Orange *p*-Naphtholbenzein	Thymol Blue Thymolphthalein Azo Violet *o*-Nitroaniline *p*-Hydroxyazobenzene	Azoviolet Bromothymol Blue *p*-Hydroxyazobenzene Thymol Blue
Electrodes	Glass-calomel Glass-silver-silver chloride Mercury-mercuric acetate	Glass-calomel Calomel-silver-silver chloride	Antimony-calomel Antimony-glass Antimony-antimony[b] Platinum-calomel Glass-calomel	Antimony-calomel Glass-calomel Glass-platinum[b]

[a] Relatively neutral solvents of low dielectric constant such as benzene, chloroform, or dioxane may be used in conjunction with any acidic or basic solvent in order to increase the sensitivity of the titration end-points. [b] In titrant.

TOCOPHEROLS—VITAMIN E

Weight-Unit Relationships

Label claims for Tocopherol products described in this National Formulary when expressed in International Units (I.U.) of Vitamin E are based on the following equivalents:

1 mg. *dl*-Alpha Tocopheryl Acetate = 1 International Unit

1 mg. *dl*-Alpha Tocopheryl Acid Succinate = 0.89 International Unit

1 mg. *dl*-Alpha Tocopherol = 1.1 International Units

1 mg. *d*-Alpha Tocopheryl Acetate = 1.36 International Units

1 mg. *d*-Alpha Tocopherol = 1.49 International Units

1 mg. *d*-Alpha Tocopheryl Acid Succinate = 1.21 International Units

REAGENTS, TEST SOLUTIONS, AND VOLUMETRIC SOLUTIONS

Specifications for many reagents and indicators, and directions for the preparation of many solutions, required in NF XIII tests and assays are included in the *Reagents, Indicators and Solutions* section of the United States Pharmacopeia, Eighteenth Revision. Specifications for those reagents, indicators, and solutions not listed in USP XVIII, but which are required in NF XIII tests and assays, are provided by the National Formulary in this section.

Reference should also be made to the *Reagents, Indicators and Solutions* section of USP XVIII for detailed instructions regarding general test procedures for *Boiling or Distilling Range, Chloride, Flame Photometry, Heavy Metals, Insoluble Matter, Iron, Loss on Drying, Phosphate, Residue on Ignition,* and *Sulfate,* unless an NF XIII page number reference is provided, in which case the NF procedure should be followed.

Reagents are substances used either as such or as constituents of solutions.

As stated in the *General Notices,* page 6, listing of reagents, indicators, and solutions in the National Formulary in no way implies that they have therapeutic merit or utility; thus, any reference to the NF in their labeling is to include the term "reagent" or "reagent grade."

Indicators are reagents used to determine the specified end-point in a chemical reaction, to measure hydrogen-ion concentration (pH), or to indicate that a desired change in pH has been effected.

Buffers used as reagent solutions are prepared as directed under *Buffers,* page 783; buffers used in standardizing pH meters are prepared as directed under *pH Determination,* page 824.

Colorimetric Solutions, abbreviated "C.S.," are solutions used in the preparation of colorimetric standards for comparison purposes.

Test Solutions, abbreviated "T.S.," are solutions of reagents in such solvents and of such definite concentrations as to be suitable for the specified purposes.

Volumetric Solutions, known also as *Standard Solutions,* are solutions of reagents of known concentration intended primarily for use in quantitative determinations. Concentrations are usually expressed in terms of normality.

N-Acetyl-L-tyrosine Ethyl Ester, $C_{13}H_{17}NO_4$—251.28—Determine suitability for use as a substrate as directed under *Trypsin Crystallized,* page 746.

Alkyl phenoxy polyethoxy ethanol—A suitable form of alkyl phenoxy polyethoxy ethanol is available as Triton X-100 from Rohm and Haas Co., Philadelphia, PA.

Alumina (*Aluminum Oxide Acid-washed for Chromatography; Chromatographic Alumina*)—A white or practically white powder. Store it in well-closed containers.

Adsorptive power—

STOCK *o*-NITROANILINE SOLUTION—Weigh 100.0 mg. of *o*-nitroaniline, and transfer it to a 50-ml. volumetric flask. Add about 30 ml. of benzene, and when solution is effected add benzene to volume,. then mix. Transfer 5.0 ml. of the solution to a 100-ml. volumetric flask, add benzene to volume, and mix.

STANDARD *o*-NITROANILINE SOLUTION—Pipet 10.0 ml. of *Stock o-Nitroaniline Solution* into a 100-ml. volumetric flask, add benzene to volume, and mix.

PROCEDURE—Weigh quickly about 2 g. of alumina to within ±5 mg. into a dry, glass-stoppered cylinder or test tube. Add 20.0 ml. of *Stock o-Nitroaniline Solution,* shake vigorously for 3 minutes, and allow to settle. Pipet 10.0 ml. of the clear, supernatant liquid into a 50-ml. volumetric flask, add benzene to volume, and mix. Measure the absorbance of this solution and of the *Standard o-Nitroaniline Solution* at 395 mμ in a suitable spectrophotometer, using benzene as the blank. Calculate the quantity, in mg., of *o*-nitroaniline adsorbed by the formula $1 - (B/A)$, in which A is the absorbance of the *Standard o-Nitroaniline Solution* and B is the absorbance of the solution treated with alumina. Not less than 300 mcg. of *o*-nitroaniline is adsorbed.

pH, page 824—To 5 g. in a glass-stoppered, 125-ml. flask add 50 ml. of water, and shake for 5 minutes. Allow to settle, decant the supernatant liquid, and determine its pH, preferably potentiometrically: the pH is between 3.0 and 5.0.

Loss on drying—Dry about 1 g., accurately weighed, at 110° for 3 hours: it loses not more than 5% of its weight.

4-Aminoantipyrine, $C_{11}H_{13}N_3O$—203.25

—Light yellow crystalline powder. One-half g. in 30 ml. of water is completely soluble and yields a clear solution.

Melting range, page 814—Between 108.0° and 110.0°.

p-**Aminophenol,** C_6H_7NO—109.13—A fine, yellowish, crystalline powder. Slightly soluble in water and in alcohol.

Melting range, page 814—Between 187° and 189°.

Ammonia Solution, Diluted—Use *Ammonia T.S.*

Ammonium Fluoride, NH_4F—37.04—Moist, white crystals; corrodes glass. Freely soluble in water; sparingly soluble in alcohol.

Insoluble matter—Five g. shows not more than 1 mg. of insoluble matter, a platinum dish being used in place of a beaker (0.02%).

Residue on ignition—Weigh quickly 5 g. in a platinum crucible, *transfer to a hood,* add 1 ml. of sulfuric acid, and ignite gently to constant weight: the residue weighs not more than 1 mg.

Acid fluoride—Dissolve 5 g. in 50 ml. of cold water in a platinum dish, add 3 drops of methyl red T.S., and titrate with 1 *N* sodium hydroxide. Each ml. of 1 *N* sodium hydroxide is equivalent to 57.04 mg. of NH_4HF_2. Not more than 1.5% is found.

Fluosilicate—Dissolve 3 g. in 15 ml. of water in a platinum dish, add 3 ml. of potassium chloride solution (1 in 5) and 15 ml. of alcohol, allow to stand for 5 minutes, then transfer the solution to a test tube and examine immediately: not more than a slight turbidity is apparent.

Heavy metals—Dissolve 1 g. in 42 ml. of water. Dilute 35 ml. of this solution to 40 ml., and add 10 ml. of hydrogen sulfide T.S.: any brown color produced is not darker than that of a control containing the remaining 7 ml. of sample solution and 20 mcg. of added Pb (30 parts per million).

Iron—To 1 g., in a platinum dish *under a hood,* add 10 ml. of hydrochloric acid, and evaporate to dryness. Add 10 ml. of acid and repeat the evaporation. To the residue add a few drops of hydrochloric acid, and dilute with water to 30 ml.: 10 ml. of this solution shows not more than 10 mcg. of Fe, the control also containing the residue from evaporation of 7 ml. of acid (30 parts per million).

Sulfate—To 1 g., in a platinum dish *under a hood,* add 10 ml. of hydrochloric acid, and evaporate to dryness. Repeat the evaporation with hydrochloric acid 4 times. Take up the final residue in 5 ml. of water, filter, wash to a volume of 50 ml., and mix: 10 ml. of this solution shows not more than 60 mcg. of SO_4(0.03%).

Ammonium Vanadate (*Ammonium Metavanadate*), NH_4VO_3 — 116.98 — A white, crystalline powder. Slightly soluble in cold water; soluble in hot water and in dilute ammonia water.

Assay—Weigh accurately about 500 mg., dissolve in 30 ml. of water, add 2 ml. of 25% sulfuric acid, and pass sulfur dioxide through the solution until reduction is complete (indicated by a bright blue color of the solution). Boil gently in a current of carbon dioxide to expel the excess of sulfur dioxide, cool, and titrate with 0.1 *N* potassium permanganate to a pink color: each ml. of 0.1 *N* potassium permanganate is equivalent to 11.7 mg. of NH_4VO_3. Not less than 98% of NH_4VO_3 is found.

Solubility in ammonia—Dissolve 1 g. in a mixture of 3 ml. of ammonia water and 50 ml. of warm water: a clear and colorless solution results.

Carbonate—To 500 mg. add 1 ml. of water and 2 ml. of diluted hydrochloric acid: no effervescence is produced.

Chloride—Dissolve 250 mg. in 40 ml. of hot water, add 2 ml. of nitric acid and allow to stand for 1 hour. Filter, and add to the filtrate 0.5 ml. of silver nitrate T.S.: the turbidity is not greater than that produced in a control to which 500 mcg. of chloride has been added.

Sulfate—Dissolve 500 mg. in 50 ml. of hot water, and add 2 ml. of diluted hydrochloric acid and 1.5 g. of hydroxylamine hydrochloride. Heat at 60° for 3 minutes, filter, cool, add to the filtrate 2 ml. of barium chloride T.S., and allow to stand for 30 minutes: no turbidity or precipitate is produced.

tert-**Amyl Alcohol,** $C_5H_{12}O$—88.15—A clear, colorless, flammable, volatile liquid with a characteristic odor. Specific gravity: about 0.81.

Boiling range—Not less than 95 percent distills between 100° and 103°.

Residue on evaporation—Evaporate 50 ml. (40 g.) on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 1.6 mg. (40 parts per million).

Acids and esters—Dilute 20 ml. with 20 ml. of alcohol, add 5.0 ml. of 0.1 *N* sodium hydroxide, and reflux gently for 10 minutes. Cool, add 2 drops of phenolphthalein T.S., and titrate the excess sodium hydroxide with 0.1 *N* hydrochloric acid: not more than 0.75 ml. of the 0.1 *N* sodium hydroxide is consumed, correction being made for the amount consumed in a blank (0.06% as amyl acetate).

Aldehydes—Shake 5 ml. with 5 ml. of potassium hydroxide solution (30 in 100) for 5 minutes in a glass-stoppered cylinder, and allow to separate: no color develops in either layer.

Anion Exchange Resin, Chloromethylated Polystyrene–divinylbenzene—A strongly basic, cross-linked resin containing quaternary ammonium groups. It consists of small, moist, yellow beads having a characteristic amine odor. It is available in the chloride form which can be converted to the hydroxide form by regeneration with a sodium hydroxide solution (1 in 4). For satisfactory regeneration a contact time of about 25 minutes is required after which it must be washed with water until neutral. Suitable for use in column chromatography.*

Anthracene, $C_{14}H_{10}$—178.24—White to off-white crystals or platelets. Darkens in sunlight. Insoluble in water; sparingly soluble in alcohol, in benzene and in chloroform.

Melting range, page 814—Between 215° and 218°.

Antimony Pentachloride, $SbCl_5$—299.02—A clear, reddish-yellow, oily, hygroscopic, caustic liquid. It fumes in moist air and solidifies by absorption of one molecule of water. Decomposed by water, soluble in dilute hydrochloric acid and chloroform. Boils at about 92° under a pressure of 30 mm. of mercury and has a specific gravity of about 2.34 at 25°.

Caution: Antimony pentachloride causes severe burns and the vapor is hazardous.

Assay (*$SbCl_5$*)—Weigh accurately a 125-ml. glass-stoppered flask, quickly introduce about 0.3 ml. of the sample and reweigh. Dissolve with 20 ml. of 20% hydrochloric acid, and add 10 ml. of potassium iodide solution (1 in 10) and 1 ml. of carbon disulfide. Titrate the liberated iodine with 0.1 *N* sodium thiosulfate. The brown color will gradually disappear from the solution and the last traces of free iodine will be collected in the carbon disulfide, giving a pink color. When this pink color disappears the end-point has been reached. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 14.95 mg. of $SbCl_5$: not less than 99.0% $SbCl_5$ is found.

Sulfate—Dissolve 4.3 ml. (10 g.) in the smallest possible quantity of hydrochloric acid. Dilute to 150 ml. with water, just neutralize with stronger ammonia water and filter. Add, to the filtrate, 2 ml. of hydrochloric acid, heat the solution to boiling, add 10 ml. of barium chloride T.S. and allow to stand overnight. If any precipitate is formed, filter, wash thoroughly with water, ignite in a tared platinum crucible, cool and weigh. The weight of the ignited precipitate (barium sulfate) should not be more than 0.0013 g. greater than the weight obtained in a complete blank test (50 parts per million SO_4). The weight of the barium sulfate ($BaSO_4$) multiplied by 0.41 is equivalent to sulfate (SO_4).

Arsenic—Add 10 ml. of a recently prepared solution of 20 g. of stannous chloride in 30 ml. of hydrochloric acid to 100 mg. of sample dissolved in 5 ml. of hydrochloric acid. Mix well, transfer to a color comparison tube, and allow to stand for 30 minutes. Any color in the solution of the sample should not be darker than that in a control containing 0.020 mg. of arsenic (As), which has been treated in the same manner as the sample, when viewed downward over a white surface (0.020%).

Iron—To the residue, from the test for *Substances not precipitated by hydrogen sulfide,* add 2 ml. of hydrochloric acid and 5 drops of nitric acid, and evaporate to dryness on the steam bath. Take up the residue with 2 ml. of hydrochloric acid and add 20 ml. of water, 30 to 50 mg. of ammonium persulfate ($(NH_4)_2S_2O_8$) and 3 ml. of ammonium thiocyanate solution (3 in 10). Any red color should not exceed that produced by 0.01 mg. of iron (Fe) in an equal volume of solution containing the quantities of the reagents used in the test with the sample, including the residue from the evaporation of 2 ml. of hydrochloric acid and 5 drops of nitric acid (10 parts per million).

Other heavy metals (*as Pb*)—Dissolve the precipitate on the filter paper, from the test for *Substances not precipitated by hydrogen sulfide,* with 75 ml. of a solution containing 6 g. of sodium sulfide ($Na_2S.9H_2O$) and 4 g. of sodium hydroxide (NaOH) dissolved in water and diluted to 100 ml. with water. Collect the filtrate in the original flask containing the remainder of the sulfide precipitate. Warm the solution to dissolve the soluble sulfides and allow the insoluble sulfides to settle. Filter, wash thoroughly with hydrogen sulfide T.S., and dissolve any precipitate remaining on the filter paper with 10 ml. of hot diluted hydrochloric acid. Dilute the filtrate to 50 ml. with water. Neutralize a 25-ml. portion of this solution with 1 *N* sodium hydroxide, and add 1 ml. of 1 *N* acetic acid and 10 ml. of hydrogen sulfide T.S. Any brown color should not exceed that produced by 0.05 mg. of lead ion in an equal volume of solution containing 1 ml. of 1 *N* acetic acid and 10 ml. of hydrogen sulfide T.S. (50 parts per million).

Substances not precipitated by hydrogen sulfide (*as SO_4*)—Dissolve 0.9 ml. (2 g.) in 5 ml. of hydrochloric acid and dilute with 95 ml. of water. Precipitate the antimony completely with hydrogen sulfide, allow the precipitate to settle, and filter, being careful not to transfer much of the precipitate to the filter paper. (Retain the precipitate.) To 50 ml. of the filtrate, add 0.5 ml. of sulfuric acid, evaporate to dryness in a tared porcelain crucible and ignite at 800° ± 25° for 15 minutes. (Retain the residue.) The weight of the ignited residue should not be more than

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* A suitable resin is that known as "Amberlite IRA-400," produced by the Rohm and Haas Company, Philadelphia, PA 19105, and available through the Mallinckrodt Chemical Works, Post Office Box 5439, St. Louis, MO 63160.

0.0010 g. greater than the weight obtained in a complete blank test (0.10%).

Azolitmin—A water-soluble coloring matter obtained from litmus. Occurs in dark violet scales. Soluble with difficulty in water, more easily soluble in hot water; insoluble in alcohol and in dilute acid; very soluble in dilute alkalies, forming deep blue solutions.

Dissolve 1 g. of azolitmin in 80 ml. of hot water, and add 20 ml. of alcohol. Add 0.1 ml. of this solution to 50 ml. of carbon dioxide-free water. The bluish red color of the liquid is changed to red by the addition of 0.05 ml. of 0.1 *N* hydrochloric acid, and this color is changed to bluish violet by the addition of 0.05 ml. of 0.1 *N* sodium hydroxide.

Barium Bromide, $BaBr_2.2H_2O$—333.18—Colorless crystals. Readily soluble in water; soluble in methanol and in alcohol.

Insoluble matter—Ten g. shows not more than 1.0 mg. of insoluble matter (0.01%).

Bromate—Dissolve 500 mg. in 10 ml. of oxygen-free water, add 2 drops of potassium iodide solution (1 in 10), 1 ml. of starch T.S., and 5 drops of 1 *N* sulfuric acid, and allow to stand at 25°: no blue color is produced within 10 minutes.

Substances not precipitated by sulfuric acid—Dissolve 5 g. in 150 ml. of water, add 1 ml. of hydrochloric acid, and heat to boiling. Add 25 ml. of diluted sulfuric acid, cool, dilute to 250 ml. with water, and allow to stand overnight. Decant through a filter, evaporate 50 ml. of the filtrate to dryness, and ignite to constant weight: the residue weighs not more than 1.0 mg. (0.1% as SO_4).

Heavy metals—Its heavy metals limit is 5 parts per million.

Chloride—Dissolve about 500 mg., previously dried at 120° to constant weight and accurately weighed, in 50 ml. of water. Add slowly and with stirring 40.0 ml. of 0.1 *N* silver nitrate, then add 2 ml. of nitric acid and 2 ml. of ferric nitrate solution (1 in 10), and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate: between 66.8 ml. and 67.8 ml. of 0.1 *N* silver nitrate is required for each g. of dried sample taken.

Beef Extract—A concentrate from beef broth obtained by extracting fresh, sound, lean beef by cooking with water and evaporating the broth at a low temperature, usually in vacuum, until a yellowish brown to dark brown, slightly acid, pasty mass, having an agreeable meat-like odor and taste, is obtained.

Solubility—A solution of 25 g. in sufficient water to make 250 ml. is nearly clear and nearly free from sediment. Use this solution for the following tests:

Total solids—Dry 10 ml. of the solution, in a tared porcelain dish containing sand or asbestos, at 105° for 16 hours: the residue is not less than 750 mg.

Residue on ignition—Incinerate the residue from the test above by heating the dish to a dull red: the residue does not exceed 30% of the total solids.

Chlorides calculated as sodium chloride—Dissolve the residue obtained in the above test in 50 ml. of water, transfer to a 100-ml. volumetric flask, add 3 drops of nitric acid and 10.0 ml. of 0.1 *N* silver nitrate, dilute to volume with water, and mix. Filter into a dry flask through a dry filter and reject the first 10 ml. of filtrate. To 50.0 ml. of the subsequent filtrate add 1 ml. of ferric ammonium sulfate T.S., and titrate with 0.1 *N* ammonium thiocyanate. Each ml. of 0.1 *N* silver nitrate is equivalent to 5.844 mg. of NaCl. The weight of chlorides calculated as sodium chloride does not exceed 6% of the total solids.

Alcohol-insoluble substances—Mix thoroughly 25 ml. of the solution with 50 ml. of alcohol, collect the precipitate on a tared filter, wash it 3 times with a mixture of alcohol and water (2:1), and dry at 105° for 2 hours: the weight of the residue does not exceed 10% of the total solids in the solution taken. (Reserve the filtrate and washings for the determination of nitrogen.)

Nitrate—Boil 10 ml. of the solution for 1 minute with 1.5 g. of activated charcoal, add water to maintain the volume, and filter: addition of 1 drop of the filtrate to 3 drops of a 1 in 100 solution of diphenylamine in sulfuric acid produces no blue color.

Nitrogen content of alcohol-soluble substances, page 821—Use a portion of the filtrate remaining from the test for *Alcohol-insoluble substances*, corresponding to 1 g. of the alcohol-soluble solids, adding 10 g. of powdered potassium sulfate and 20 ml. of sulfuric acid to the 500-ml. Kjeldahl flask. The amount of nitrogen found is not less than 60 mg.

Nitrogen as ammonia—To 100 ml. of the solution of the Extract, in a 500-ml. Kjeldahl flask, add 5 g. of barium carbonate and 100 ml. of water, and distil the ammonia into 50.0 ml. of 0.1 *N* sulfuric acid. The amount of ammonia does not exceed 0.35% of the total solids in the solution taken.

***p*-Benzoquinone** (*Quinone*), $C_6H_4O_2$—108.10—A yellow, crystalline powder. Penetrating odor resembling that of chlorine. Very slightly soluble in water; soluble in ether and in alcohol.

Melting range, page 814—Between 113° and 116°.

***N*-Benzoyl-L-arginine Ethyl Ester Hydrochloride,** $C_{15}H_{22}N_4O_3.HCl$—342.83—Determine suitability for use as a substrate as directed under *Trypsin Crystallized,* page 746.

Benzyl Alcohol, $C_6H_5CH_2OH$—108.14—A clear, colorless liquid having a slight, characteristic odor. On exposure to air it slowly oxidizes to benzaldehyde and benzoic acid. Soluble in water. Miscible with alcohol, with chloroform, and with ether. Specific gravity about 1.04. Store it in tight containers, protected from light.

Boiling range—Not less than 94% distils between 202° and 206°.

Solubility in water and reaction—Shake 2.0 ml. with 60 ml. of water: a clear solution, which is neutral to litmus, results.

Aldehyde—Shake 5 ml. with 5 ml. of potassium hydroxide T.S., and allow to stand for 1 hour: the water layer is not colored yellow.

Chlorine—Moisten a clean, freshly ignited copper spiral with the sample, and heat in a nonluminous flame: the flame is not colored green.

Blood (for carbon monoxide test in gases)—Use *oxalated* or *defibrinated blood* of dogs, sheep, cattle, or human beings within 24 hours after bleeding. Prepare *oxalated blood* by adding 10 mg. of sodium oxalate to each ml. of the freshly drawn blood.

Bovine Albumin—Collect blood from beef cattle in a vessel containing sodium citrate solution (8 in 100) in the proportion of 1 volume for each 19 volumes of blood to be collected. Centrifuge the collected blood and siphon the plasma, and promptly cool it to just above its freezing temperature. Maintain the temperature between 0° and −5° during the entire processing to prevent denaturation of the albumin.

Measure the plasma, and slowly add 883 ml. of dilute alcohol (53% *v/v*) for each 1000 ml. of plasma. Take special care in adding the alcohol to ensure that heat evolved is removed rapidly enough to prevent a temperature rise. Filter off the precipitate formed, and for each 1000 ml. of filtrate slowly add a mixture of 1130 ml. of dilute alcohol (53% *v/v*) and 76 ml. of 1.0 *M* sodium acetate which has been buffered with acetic acid to pH 5.1 measured when diluted 1 to 20. A 1 in 5 dilution of the final mixture has a pH of 5.8. Filter off the precipitated globulins, and adjust the filtrate to pH 5.2 by the addition of 1.0 *M* sodium acetate which has been buffered with acetic acid to pH 4.0 measured when diluted 1 in 20. Filter off the precipitated albumin, and remove it from the filter paper, using water if necessary. Freeze the resulting mixture, and dry in vacuum from the frozen state.

Bromophenol Blue (**3′,3′′,5′,5′′**-*tetrabromophenolsulfonphthalein*)—[Note: This specification applies both to the free acid form and to the salt form of this indicator.]

Insoluble matter—If the indicator is the acid form, dissolve 0.1 g. in 100 ml. of alcohol. If the indicator is the salt form, dissolve 0.1 g. in 100 ml. of water. Not more than a faint trace of turbidity or insoluble matter should remain. Reserve the solution for the test for *Visual transition interval*.

Visual transition interval—Dissolve 1 g. of potassium chloride in 100 ml. of water. Adjust the pH of the solution to 3.00 (using a pH meter) with 0.01 *N* acid. Add 0.10 to 0.30 ml. of the 0.1 percent solution of the indicator reserved from the test for *Insoluble matter*. The color of the solution should be yellow with a slight greenish hue. Titrate the solution with 0.01 *N* sodium hydroxide to a pH of 3.4 (using the pH meter). The color of the solution should be green. Continue the titration to pH 4.6. The color of the solution should be blue. Not more than 13.0 ml. of 0.01 *N* sodium hydroxide should be consumed in the entire titration.

tert-**Butyl Alcohol,** $(CH_3)_3COH$—74.12—A colorless liquid or solid. Miscible with water, with alcohol, and with ether.

Boiling range—Not less than 95% distils between 81° and 83°.

Melting range, page 814—Between 24° and 26°.

Specific gravity, page 866—The specific gravity is between 0.778 and 0.782.

Calcium Citrate, $Ca_3(C_6H_5O_7)_2.4H_2O$—570.51—A white, odorless, crystalline powder. Slightly soluble in water, insoluble in alcohol; soluble in diluted hydrochloric and nitric acids. To 15 ml. of hot diluted sulfuric acid add in small portions and with stirring about 500 mg. of calcium citrate. Boil the mixture for 5 minutes, and filter while hot: the cooled filtrate responds to the identification test for *Citrate,* page 808.

Assay—Weigh accurately about 400 mg. of the salt, previously dried at 150° to constant weight, and transfer to a 250-ml. beaker. Dissolve the sample in 150 ml. of water containing 2 ml. of diluted hydrochloric acid, add 15 ml. of sodium hydroxide T.S. and 250 mg. of hydroxy naphthol blue indicator, and titrate with 0.05 *M* disodium ethylenediaminetetraacetate until the solution turns deep blue in color. Each ml. of 0.05 *M* disodium ethylenediaminetetraacetate is equivalent to 8.307 mg. of $Ca_3(C_6H_5O_7)_2$. Between 97.5 and 101% is found.

Calcium oxide and carbonate—Triturate 1 g. of calcium citrate with 5 ml. of water for 1 minute: the mixture does not turn red litmus paper blue. Then add 5 ml. of warm diluted hydrochloric acid: only a few isolated bubbles escape.

Hydrochloric acid-insoluble matter—Dissolve 5 g. by heating with a mixture of 10 ml. of hydrochloric acid and 50 ml. of water for 30 minutes: not more than 2.5 mg. of insoluble residue remains (0.05%).

Loss on drying—Dry it at 150° to

constant weight: it loses between 12.2 and 13.3% of its weight.

Arsenic, page 777—Proceed with 1.67 g. as directed for organic compounds (6 parts per million As).

Heavy metals—Dissolve 1 g. in 20 ml. of water and 2 ml. of hydrochloric acid, adjust to a pH between 3 and 4 with ammonium hydroxide, and dilute to 40 ml. Add 10 ml. of hydrogen sulfide T.S. Any brown color produced is not darker than that in a control containing 20 mcg. of added lead (Pb), 2 ml. of diluted acetic acid, and 10 ml. of hydrogen sulfide T.S. in a 50 ml. volume (20 parts per million).

Calcium Nitrate, $Ca(NO_3)_2.4H_2O$—236.15—Colorless, deliquescent crystals having a slight odor of nitric acid. Soluble in water, acetone, and alcohol.

Acidity—Dissolve 10 g. in 50 ml. of water, add 3 drops of phenolphthalein T.S., and titrate with 0.1 *N* sodium hydroxide to the production of a pink color: not more than 0.15 ml. of the 0.1 *N* sodium hydroxide is required (0.01%).

Barium—Dissolve 2 g. in 15 ml. of water, add 2 g. of sodium acetate and 1 drop of glacial acetic acid, and filter if necessary. Prepare a control containing 2 g. of sodium acetate, 1 drop of glacial acetic acid, and 0.1 mg. of added Ba, in an equal volume of solution, and add 2 ml. of potassium dichromate solution (1 in 10): any turbidity produced within 10 minutes does not exceed that produced in the control (50 parts per million).

Chloride—The chloride in 1 g. corresponds to not more than 20 mcg. of Cl (20 parts per million).

Heavy metals—The heavy metals limit is 5 parts per million.

Iron—Two g. shows not more than 10 mcg. of Fe (5 parts per million).

Insoluble and ammonium hydroxide precipitate—Heat to boiling a solution of 20 g. in 100 ml. of water, and add carbonate-free stronger ammonia water until the solution is slightly alkaline. Boil 5 minutes, and if any precipitate is formed, filter, and wash with hot water. Redissolve the precipitate with a few ml. of hot diluted hydrochloric acid, and boil the solution (about 20 ml.) for 1 to 2 minutes. Make the solution alkaline with stronger ammonia water, and filter through the same paper. Wash the precipitate thoroughly, ignite in a tared crucible, cool, and weigh: the residue weighs not more than 1.0 mg. (50 parts per million).

Magnesium and alkali salts—To 2 g. dissolved in 100 ml. of water add 5 ml. of hydrochloric acid and a few drops of methyl red T.S., and heat to boiling. Add, dropwise and with stirring, 100 ml. of warm ammonium oxalate T.S., heat to 70° to 80°, and add ammonia T.S. dropwise, until the solution is alkaline to methyl red T.S. Dilute to 250 ml., allow to stand 1 hour, and filter. To 125 ml. of the filtrate add 0.5 ml. of sulfuric acid, evaporate to 30 ml., and cool. Add 25 ml. of nitric acid, and evaporate to dryness. Take up the residue in a few ml. of water, transfer to a tared evaporating dish, evaporate to dryness, and heat the residue on a hot plate until fumes of SO_3 are no longer evolved. Ignite at 700° to 750°, cool, and weigh: the residue weighs not more than 2.0 mg. (0.2%).

Sulfate—To 2 g. in a small beaker, add 6 ml. of hydrochloric acid, and evaporate on a steam bath to dryness. Take up the residue in 20 ml. of water and 1 ml. of 1 *N* hydrochloric acid, filter if necessary, and add 2 ml. of barium chloride T.S. Any turbidity produced within 10 minutes is not greater than that in a control containing, in equal volume, 400 mcg. of added sulfate (SO_4), 1 ml. of 1 *N* hydrochloric acid, and 2 ml. of barium chloride T.S. (0.02%).

Capryl Alcohol (*2-Octanol*), $CH_3(CH_2)_5$-$CHOHCH_3$—130.23—A clear, colorless, oily liquid, having a pungent, aromatic odor. Insoluble in water. Miscible with alcohol, with benzene, and with ether. Specific gravity: about 0.82.

Boiling range—Not less than 95% distils between 178° and 181°.

Refractive index, page 858—Its refractive index at 20° is between 1.424 and 1.426.

Residue on evaporation—Evaporate 12 ml. on a steam bath, and dry it at 150° for 2 hours: the residue weighs not more than 1.0 mg. (0.01%).

Water—Mix 5 ml. with 20 ml. of solvent hexane: the mixture is clear.

Cation Exchange Resin, Styrene-divinylbenzene—A strongly acidic, cross-linked sulfonated resin containing about 2% divinylbenzene. It consists of white to light tan colored beads which may be relatively free flowing. It is available in the hydrogen form in the 25 to 50, 45 to 100 and 80 to 270 mesh sizes. It can be regenerated to the hydrogen form by treating with a hydrochloric acid solution (5 in 100). For satisfactory regeneration a contact time of at least 30 minutes is required after which it must be washed free of excess acid. It is insoluble in water, methanol and acetonitrile. Suitable for use in column chromatography.*

Moisture content of fully regenerated and expanded resin—Transfer 10 to 12 ml. of the resin (as received) to a flask and convert it completely to the hydrogen form by stirring with 150 ml. of hydrochloric acid solution (5 in 100) for not less than 30 minutes. Decant the acid and wash the resin in the same manner with water until the wash water is neutral to litmus paper (pH 3.5).

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* A suitable resin is that known as "Dowex 50W-X2," produced by The Dow Chemical Company, Midland, MI 48640 and available through J. T. Baker Chemical Company, Phillipsburg, NJ 08865.

Transfer 5 to 7 ml. of the regenerated resin to a glass filtering crucible and remove only the excess surface water by very careful suction filtration. Transfer the conditioned resin to a tared weighing bottle and weigh. Dry in a vacuum oven at 100° to 105° and 50 mm. of mercury for 16 hours. Transfer from the vacuum oven to a desiccator and cool to room temperature. Reweigh. The loss in weight is between 75 and 83%.

Total wet volume capacity—Transfer 3 to 5 ml. of the regenerated, undried (see *Moisture content* above) resin to a 5-ml. graduated cylinder and fill it with water. Remove any air bubbles from the resin bed with a stainless steel wire and settle the resin to its minimum volume by tapping the graduated cylinder. Record the volume of the resin.

Transfer the resin to a 400-ml. beaker. Add about 5 g. of sodium chloride and titrate, stirring well, with 0.1 N sodium hydroxide to the blue end-point of bromothymol blue (pH 7.0).

$$\frac{\text{net ml. NaOH} \times N}{\text{ml. of resin}} = \text{milliequivalents/ml.}$$

The total wet volume capacity of the resin is more than 0.6 milliequivalents per ml.

Wet screen analysis—The purpose of this test is to properly identify the mesh size of the resin. To obtain an accurate screen analysis would require special apparatus and technique.

Add 150 ml. of resin to 200 ml. of water in an appropriate bottle and allow it to stand at least four hours to completely swell the resin.

Transfer by means of a graduated cylinder 100 ml. of settled and completely swollen resin to the top screen of a series of the designated U.S. Standard 20.3-cm. brass screens. Thoroughly wash the resin on each screen with a stream of water until the resin is completely classified, collecting the wash water in a suitable container. Wash the beads remaining on the respective screens back into the 100-ml. graduate and record the volume of settled resin on each screen. At least 70% of the resin will be within the specified mesh size.

Ceric Sulfate, $Ce(SO_4)_2$ with a variable amount of water—It contains also sulfates of the other associated earths. Yellow to orange-yellow crystals or crystalline powder. Almost insoluble in cold water; slowly soluble in cold dilute mineral acids; more readily soluble when heated with these solvents.

Assay—Weigh accurately about 800 mg., transfer to a flask, add 25 ml. of water and 3 ml. of sulfuric acid, and warm until dissolved. Cool, and add 60 ml. of a mixture of 1 volume of phosphoric acid and 20 volumes of water. Add 25 ml. of potassium iodide solution (1 in 10), stopper the flask, and allow to stand for 15 minutes. Then titrate the liberated iodine with 0.1 N sodium thiosulfate in an atmosphere of carbon dioxide, adding starch T.S. as the indicator: each ml. of 0.1 N sodium thiosulfate is equivalent to 33.22 mg. of $Ce(SO_4)_2$. Not less than 80% is found.

Chloride—Dissolve 1 g. in a mixture of 5 ml. of nitric acid and 4 ml. of water. Filter if not clear, and divide into two equal portions. To one portion add 1 ml. of silver nitrate T.S., allow to stand for 10 minutes, filter until clear, and use for the control. To the other portion add 1 ml. of silver nitrate T.S.: the resulting turbidity in the second portion does not exceed that produced by adding 50 mcg. of Cl to the control (0.01%).

Heavy metals—Heat 500 mg. with a mixture of 10 ml. of water and 0.5 ml. of sulfuric acid until dissolved. Cool, dilute with water to 50 ml., and saturate with hydrogen sulfide: a precipitate of sulfur forms that is white or not darker than pale yellow.

Iron—Dissolve 100 mg. in a mixture of 5 ml. of water and 2 ml. of hydrochloric acid, warming if necessary, and cool. Dilute with water to 25 ml. in a stoppered cylinder, and add 5 ml. of ammonium thiocyanate T.S. and 25 ml. of ether. Shake gently but well, and allow to separate: the pink color in the ether layer is not darker than that produced by diluting a quantity of standard iron solution containing 20 mcg. of Fe with 2 ml. of hydrochloric acid and sufficient water to measure 25 ml., then treating this solution with ammonium thiocyanate T.S. and ether in the same manner as for the ceric sulfate solution (0.02%).

Chloranil (*Tetrachlorobenzoquinone*), $C_6Cl_4O_2$—245.88—Golden yellow leaflets. Insoluble in water; slightly soluble in alcohol; soluble in ether. Dissolves in sodium hydroxide solutions, forming a violet-red solution.

Melting range, page 814—When determined in a sealed tube in a bath preheated to 270°, it melts at about 295°.

Residue on ignition—The residue on ignition from 200 mg. is negligible.

Chlorinated Lime—A white or grayish white powder, having the odor of chlorine. It rapidly decomposes on exposure to air. It is partially soluble in water and in alcohol.

Assay—Transfer to a mortar about 4 g., accurately weighed in a tared weighing bottle, using 50 ml. of water. Triturate thoroughly, and pour the mixture into a 1000-ml. volumetric flask. Rinse the mortar with water into the flask, dilute to volume, and mix. Add to 100 ml. of the mixture 1 g. of potassium iodide and 5 ml. of acetic acid, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 3.545 mg. of available chlorine (Cl). It shows not less than 30% of available chlorine.

Preserve in air-tight containers in a cool, dry place.

***p*-Chloroaniline,** $ClC_6H_4NH_2$—127.57—White or grayish white crystals. Slightly soluble in water; very soluble in alcohol; soluble in most organic solvents.

Melting range, page 814—It melts between 70° and 72° and its acetyl derivative melts within a 2° range between 169° and 178°.

Chloride—To a solution of 50 mg. in 5 ml. of diluted alcohol add 3 drops each of diluted nitric acid and of silver nitrate T.S.: no turbidity is produced in 1 minute.

Sensitiveness—Dissolve 10 mg. in 100 ml. of water. Dilute 0.5 ml. of the solution with water to 5 ml. Add 1 drop of hydrochloric acid, mix, and add 1 drop of sodium nitrite solution (1 in 10). Cool to about 15°, add 2 ml. of sodium carbonate T.S., then add 0.5 ml. of 2-naphthol-3,6-sodium disulfonate solution (1 in 10): a deep red color is produced.

Residue on ignition—The residue on ignition from 100 mg. is negligible.

***p*-Chlorophenol,** ClC_6H_4OH—128.56—A white to pale straw-colored, crystalline solid, possessing the odor typical of a chlorinated phenol. Very soluble in acetone, benzene, ether, and methanol; sparingly soluble in water.

Melting range, page 814—Between 42° and 44°.

Boiling range—Not less than 90% distils between 218.5° and 221.5°.

Assay—Weigh accurately about 200 mg. into a 100-ml. beaker, and dissolve in 25 ml. of water, using enough sodium hydroxide solution (1 in 50) to ensure solution. Transfer the solution to a 500-ml. volumetric flask, using water for washing (do not use heat). Dilute with water to about 100 ml., and add 25.0 ml. of 0.1 *N* potassium bromide-potassium bromate and 10 ml. of hydrochloric acid. Immediately stopper the flask and swirl vigorously for 1 to 3 minutes. Remove the stopper, quickly add 5 ml. of potassium iodide solution (1 in 5), taking care to avoid loss of bromine, immediately stopper the flask and shake thoroughly for about 1 minute. Remove the stopper, rinse down the neck of the flask with water, and titrate with 0.1 *N* sodium thiosulfate, adding starch T.S. as the end-point is neared. Each ml. of 0.1 *N* potassium bromide-potassium bromate is equivalent to 6.43 mg. of ClC_6H_4OH. Not less than 99% is found.

Chromium Trioxide, CrO_3—99.99—Dark purplish red crystals, often needle-like, or in flakes. Very soluble in water. It is deliquescent, and is destructive to animal and vegetable tissues.

Caution: Chromium Trioxide should not be brought into intimate contact with organic substances or other reducing agents, as serious explosions are likely to result.

Assay—Weigh accurately about 5 g., transfer to a 1-liter volumetric flask, dissolve in water, and dilute with water to volume. Mix the solution thoroughly, transfer a 25.0-ml. aliquot to a glass-stoppered flask, and dilute with 100 ml. of water. Add 5 ml. of dilute sulfuric acid (1 in 2) and 3 g. of potassium iodide, and allow to stand in the dark for 15 minutes. Dilute with 100 ml. of water and titrate the liberated iodine with 0.1 *N* sodium thiosulfate, adding starch indicator solution near the end-point. Correct for a complete blank test. Each ml. of 0.1 *N* sodium thiosulfate corresponds to 3.333 mg. of CrO_3. Not less than 98.0% is found.

Insoluble Matter—Dissolve 10 g. in 100 ml. of water, heat to boiling, and digest in a covered beaker on the steam bath for 1 hour. Filter through a tared filtering crucible, wash thoroughly, and dry at 105°. The weight of the residue should not exceed 0.0010 g. (0.010%).

Chloride—Dissolve 1 g. in water, filter if necessary through a chloride-free filter, and dilute with water to 50 ml. To 10 ml. of this solution add 1.5 ml. of stronger ammonia water and 1 ml. of silver nitrate T.S., mix, and add 2 ml. of nitric acid. Any turbidity should not exceed that produced in a standard containing 1 ml. of stronger ammonia water, 1 ml. of silver nitrate T.S., 2 ml. of nitric acid, and 0.01 mg. of added chloride ion (Cl) (50 parts per million). The comparison is best made by superimposing a tube containing 10 ml. of the sample solution, 1.5 ml. of stronger ammonia water, and 2 ml. of nitric acid over the tube containing the standard turbidity, and placing a similar tube containing 11 ml. of water, 1 ml. of stronger ammonia water, and 2 ml. of nitric acid below the tube containing the sample and added reagents. Both turbidities are thus viewed through the same depth and color of solution. The comparison tubes may be machine-made vials, long style, of about 20-ml. capacity.

Sulfate—Dissolve 10 g. in 350 ml. of water and add 5 g. of sodium carbonate. Heat to boiling and add 35 ml. of a solution containing 1 g. of barium chloride and 2 ml. of hydrochloric acid in 100 ml. of solution. Digest in a covered beaker on the steam bath for 2 hours and allow to stand overnight. If a precipitate is formed, filter, wash thoroughly, and ignite. Fuse the ignited precipitate with 1 g. of sodium carbonate. Extract the fused mass with water and filter out the insoluble residue. Add 5 ml. of hydrochloric acid to the filtrate, dilute with water to about 200 ml., heat to boiling, and add 10 ml. of alcohol. Digest on the steam bath until the reduction of chromate is complete, as indicated by the change to a clear green or colorless solution. Neutralize the solution with stronger ammonia water and add 2 ml. of hydrochloric acid. Heat to boiling and add 10 ml. of barium chloride T.S. Digest in a covered beaker on the steam bath for 2 hours and allow to stand overnight. Filter, wash thoroughly, and ignite. The weight of the precipitate should not be more than 1.2 mg. greater than the weight obtained in a complete blank test (50 parts per million).

Iron, aluminum, barium—Dissolve 5 g. in 100 ml. of water, and add 10 ml. of stronger ammonia water and 1 ml. of 30% hydrogen peroxide. Heat the solution to boiling and boil gently for 5 minutes. Cool, filter, and wash the precipitate with water. Dissolve the precipitate in warm dilute hydrochloric acid (1 in 2), collecting the filtrate in the original beaker. Dilute the filtrate with water to about 30 ml., adjust to pH 7.0 with stronger ammonia water, and add 0.5 ml. of 30 percent hydrogen peroxide. Heat the solution to boiling and boil gently for 5 minutes. Cool, filter and ignite. The weight of the residue should not exceed 1.5 mg. (0.03%).

Cyclohexylamine, $\overline{CH_2(CH_2)_4C}HNH_2$—99.18—A clear, colorless to slightly yellow liquid with a strong characteristic amine odor. Strong base. It is miscible with water, alcohol, ether, esters and ketones. Refractive index about 1.456; flash point about 30°.

Specific gravity, page 866—Between 0.8645 and 0.8655.

pH of (1 in 10,000) solution, page 824—about 10.5.

Boiling range—Not less than 90 percent distils between 134° and 135°.

Diastatic Enzyme Preparation—Determine suitability for use in preparation of the *Assay Preparation* in the *Assay for Thiamine* under *Dried Yeast,* page 764.

Diatomaceous Silica, Calcined*—A form of silica (SiO_2) consisting of fused frustules and fragments of diatoms. It is an amorphous, fine, light pink or white powder. Insoluble in water, in acids, and in dilute solutions of alkali hydroxides.

Loss on ignition—Weigh accurately about 4 g. and ignite to constant weight: it loses not more than 10% of its weight.

Organic impurities—It does not darken appreciably upon ignition.

Loss on drying—Weigh accurately about 4 g. and dry at 110° for 2 hours: it loses not more than 2% of its weight.

2,5-Dichloroaniline, $Cl_2C_6H_3.NH_2$—162.02—White, needle-like crystals. Soluble in alcohol and in ether; slightly soluble in water.

Melting range, page 814—Between 49° and 50°.

Di(2-ethylhexyl) Sebacate (Dioctyl Sebacate), $C_8H_{17}OOC(CH_2)_8COOC_8H_{17}$—426.66—A pale straw-colored liquid. Insoluble in water. Refractive index about 1.448. Suitable for use in gas chromatography.**

Specific gravity, 20°/20°, page 866—Between 0.913 and 0.917.

Boiling range—Between 243° and 248° at 5 mm. Hg.

Diiodofluorescein, $C_{20}H_{10}I_2O_5$—584.11—Orange-red, odorless powder. Slightly soluble in water, soluble in alcohol and in solutions of alkali hydroxides.

Residue on ignition—Ignite 200 mg. with 5 drops of sulfuric acid: the weight of the residue does not exceed 1.0 mg. (0.5%).

Sensitiveness—Weigh accurately about 100 mg. of potassium iodide, previously dried at 105° to constant weight, and dissolve it in 50 ml. of water. Add 1 ml. of diiodofluorescein T.S. prepared from the test sample and 1 ml. of glacial acetic acid, and titrate with 0.1 *N* silver nitrate until the color of the precipitate changes from brownish red to a bluish red. The volume of 0.1 *N* silver nitrate consumed should not be in excess of 0.1 ml. over the calculated volume, based on the KI content of the dried potassium iodide determined as follows. Dissolve about 500 mg. of potassium iodide, accurately weighed, in about 10 ml. of water, and add 35 ml. of hydrochloric acid and 5 ml. of chloroform. Titrate with 0.05 *M* potassium iodate until the purple color of iodine disappears from the chloroform. Add the last portions of the iodate solution dropwise, agitating vigorously and continuously. After the chloroform has been decolorized, allow the mixture to stand for 5 minutes. If the chloroform develops a purple color, titrate further with the iodate solution. Each ml. of 0.05 *M* potassium iodate is equivalent to 16.60 mg. of KI.

p-**Dimethylaminoazobenzene,** *Methyl Yellow, Butter Yellow,* $C_6H_5N:NC_6H_4N(CH_3)_2$—225.30—Yellow leaflets or yellow crystalline powder.

Solubility—Insoluble in water, sparingly soluble in chloroform, in ether, or in fatty oils. Dissolve 100 mg. in 20 ml. of alcohol:

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* Suitable grades of calcined diatomaceous silica are Chromosorb P and Chromosorb W available from Johns-Manville Corp., 270 Madison Ave., New York, NY 10016.

** A suitable grade is that known as Dioctyl Sebacate, produced by the Harchem Division, Wallace and Tiernan, Inc., 25 Main Street, Belleville, NJ 07101.

the solution is complete or practically so and clear.

Melting range, page 814—Between 115° and 117°.

Residue on ignition—Yields not more than 0.1% of its weight upon ignition.

Sensitiveness—Add 0.05 ml. of an alcohol solution (1 in 200) and 2 g. of ammonium chloride to 25 ml. of carbon dioxide-free water: the lemon-yellow color of the solution is changed to orange by the addition of 0.05 ml. of 0.1 *N* hydrochloric acid and restored on the subsequent addition of 0.05 ml. of 0.1 *N* sodium hydroxide.

p-Dimethylaminocinnamaldehyde, $(CH_3)_2NC_6H_4CH{:}CHCHO$ — 175.23 — Orange-yellow powder. Soluble in acetone, in alcohol, and in benzene.

Melting range, page 814—Between 132° and 136°.

Dimethylaniline, $C_6H_5N(CH_3)_2$—121.18—A clear, colorless liquid when freshly distilled, but acquiring a reddish to reddish brown color. Specific gravity: 0.960. Freezing point about 2°. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in dilute mineral acids.

Boiling range—Distil 100 ml.: the difference between the temperatures observed when 1 ml. and 95 ml. have distilled, is not more than 2.5°. Its boiling temperature at 760 mm. of Hg pressure is 194.2°.

Hydrocarbons—Dissolve 5 ml. in a mixture of 10 ml. of hydrochloric acid and 15 ml. of water: a clear solution results and remains clear on cooling to about 10°.

Aniline or monomethylaniline—Place 5 ml. in a glass-stoppered flask, add 5 ml. of a solution of acetic anhydride in benzene (1 in 10), mix, and allow to stand for 30 minutes. Add 30.0 ml. of 0.5 *N* sodium hydroxide, shake the mixture, add phenolphthalein T.S., and titrate with 0.5 *N* hydrochloric acid. Perform a blank determination, and make any necessary correction. Not more than 0.3 ml. of sodium hydroxide is consumed by the sample.

Dimethyl Polysiloxane Fluid 350—A clear, colorless, essentially odorless, oily silicone liquid, having a viscosity at 25° of 350 centistokes. Suitable for use as an adsorbent in gas-liquid chromatography.*

Dimethyl Sulfoxide, Spectro-grade—Use USP XVIII Dimethyl Sulfoxide reagent meeting the following additional specifications:

Assay—Inject an appropriate sample (about 0.1 µl.) into a suitable gas chromatograph (see page 787) equipped with a thermal conductivity detector, and obtain the chromatogram. Under typical conditions, the instrument contains a 2 m. × 3-mm. (inside diameter) glass column packed with polyethylene glycol 20,000, 20 percent on calcined chromatographic siliceous earth, 80–100 mesh. The column is maintained at 95°, and the injection port and the thermal conductivity detector block are maintained at 180°. Helium is used as the carrier gas at a flow rate of about 50 ml. per minute. The area of the symmetric dimethyl sulfoxide peak is at least 99 percent of the total peak area.

Ultraviolet absorption—Determine the ultraviolet absorbance of the sample in a 1-cm. cell from 400 mµ to 262 mµ, using water as the blank: the absorbance does not exceed 1.00 at 262 mµ, 0.360 at 270 mµ, 0.080 at 300 mµ, and 0.010 in the range of 340 mµ to 400 mµ. The absorbance curve should be smooth and should not show extraneous absorbances within the range observed.

1-Dodecanol (Dodecyl Alcohol), $CH_3(CH_2)_{11}OH$—186.34—A clear, colorless liquid. Crystallizes as leaflets from dilute alcohol solution.

Melting range, page 814—Between 23° and 25°.

Ethyl Oxide (*Solvent Ether*), $C_4H_{10}O$—74.12—A transparent, dolorless, mobile liquid, having a characteristic odor. It is slowly oxidized by the action of air, moisture, and light, with the formation of peroxides. It boils at about 35°. *It is highly volatile and flammable. Its vapor, when mixed with air and ignited, may explode violently.* It dissolves in about 12 times its volume of water with slight contraction of volume. It is miscible with alcohol, with benzene, with chloroform, with solvent hexane, and with fixed and volatile oils.

Preserve in partly filled, tight, light-resistant containers, remote from fire. It is recommended that it be kept at a temperature not exceeding 25°.

Specific gravity, page 866—The specific gravity of Ethyl Oxide is not less than 0.713 and not more than 0.716 (indicating 96 to 98 percent of $C_4H_{10}O$).

Acidity—To 10 ml. of 80 percent alcohol in a 50-ml. glass-stoppered flask, add 0.5 ml. of phenolphthalein T.S., and just sufficient 0.02 *N* sodium hydroxide to produce a pink color which persists after shaking the mixture for 30 seconds. Then add 25 ml. of Ethyl Oxide, stopper the flask, mix gently, and again add 0.02 *N* sodium hydroxide until the pink color persists after shaking the mixture for 30 seconds: not more than an additional 0.4 ml. of 0.02 *N* sodium hydroxide is required for neutralization.

Nonvolatile residue—Allow 50 ml. to evaporate spontaneously from a tared dish, and dry at 105° for 1 hour: the weight of the residue does not exceed 1 mg.

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* A suitable grade of dimethyl polysiloxane fluid 350 is "Silicone Fluid SF-96 (350)" available from the General Electric Company, Silicone Products Department, Mechanicsville Road, Waterford, NY 12188.

Foreign odor—Place 10 ml. in a clean, dry, evaporating dish, and allow it to evaporate spontaneously to a volume of about 1 ml.: no foreign odor is perceptible. Transfer this residue to a piece of clean, odorless, absorbent paper: no foreign odor is perceptible when the last traces of Ethyl Oxide evaporate from the paper.

Aldehyde—Shake 10 ml. occasionally during 2 hours with 1 ml. of potassium hydroxide T.S. in a glass-stoppered cylinder of colorless glass protected from light: no color is produced in either liquid.

Peroxide—Shake 10 ml. for 1 minute with 1 ml. of a freshly prepared solution of potassium iodide (1 in 10) in a glass-stoppered cylinder of colorless glass: when viewed transversely against a white background, no color is observed in either liquid.

Ethylenediamine, $NH_2CH_2CH_2NH_2$—60.10—Use *Ethylenediamine* USP XVIII.

Ferric Sulfate, $Fe_2(SO_4)_3.xH_2O$—Grayish white, hygroscopic powder, or fawn-colored pearls, slowly soluble in water.

Insoluble matter—Ten g., dissolved in a mixture of 100 ml. of water and 5 ml. of sulfuric acid, shows not more than 2 mg. of insoluble matter (0.02%).

Chloride—Dissolve 1 g. by warming with a mixture of 10 ml. of water and 1 ml. of nitric acid, add 4 ml. of additional nitric acid, and dilute with water to 50 ml. To 25 ml. add 1 ml. of phosphoric acid and 1 ml. of silver nitrate T.S. Any turbidity does not exceed that produced in a control containing 0.01 mg. of chloride ion (Cl), 1 ml. of nitric acid, 1 ml. of phosphoric acid, and 1 ml. of silver nitrate T.S. (20 parts per million).

Ferrous iron—Dissolve 4 g. by warming with 50 ml. of dilute sulfuric acid (1 in 10), cool, and titrate with 0.1 *N* potassium permanganate: not more than 0.16 ml. is required to produce a permanent pink color (0.02% as Fe^{++}).

NOTE: Since the reagents used in the tests for *Copper* and *Zinc* may contain excessive amounts of copper and zinc, they should first be purified by extracting with dithizone extraction solution (see page 813).

Copper—Dissolve 1.2 g. in 100 ml. of water. To 10 ml. add 50 ml. of a solution containing 5 g. of ammonium tartrate and 5 ml. of stronger ammonia water. Add 10 ml. of dithizone standard solution, shake for 2 minutes, draw off the dithizone layer, and compare the pink color with that in a control containing 6 mcg. of copper ion (Cu) and treated exactly as the 10 ml. portion of sample solution. If the color in the sample solution is less than that in the control, then the sample contains less than the limit of both *Copper* and *Zinc.* If the color in the sample solution is more than that in the control, add 15 ml. of dilute hydrochloric acid (1 in 250), and shake for 2 minutes. Draw off the dithizone solution, and shake with a second 15 ml. of dilute hydrochloric acid (1 in 250) for 2 minutes. Draw off the dithizone, combine the two acid extracts, and reserve for the *Zinc* test. Any pink color in the dithizone solution is not darker than that in the control solution treated exactly as the sample solution (50 parts per million).

Zinc—To the combined acid extracts saved from the *Copper* test, add 0.5 *M* sodium acetate to bring the pH between 5.0 and 5.5, and then add 1 ml. of 0.1 *N* sodium thiosulfate. Add 10 ml. of dithizone standard solution, shake for 2 minutes, and allow the layers to separate. Draw off the dithizone and discard the water layer. Any pink color is not greater than that in a control prepared by adding 6 mcg. of zinc ion (Zn) to the combined acid extracts from the control used in the test for *Copper* (50 parts per million).

Nitrate—Dissolve 10 g. in 100 ml. of dilute sulfuric acid (1 in 100), heat to boiling, and pour, slowly, into a mixture of 140 ml. of water and 50 ml. of stronger ammonia water. Filter through a folded filter while still hot, wash with hot water until the volume of filtrate is 300 ml., mix, and cool. To 15 ml. of this solution add 1 ml. of sodium chloride solution (1 in 200), 0.10 ml. of indigo carmine T.S., and 15 ml. of sulfuric acid. The blue color is not completely discharged at the end of 5 minutes (0.01%).

Substances not precipitated by ammonia—Evaporate to dryness 30 ml. of the filtrate obtained in the test for *Nitrate,* and ignite gently: the weight of residue does not exceed 1 mg. (0.01%).

Assay—Weigh accurately about 700 mg., and dissolve it in a mixture of 50 ml. of water and 3 ml. of hydrochloric acid in a glass-stoppered flask. Add 3 g. of potassium iodide and let stand in the dark for 30 minutes. Then dilute with 100 ml. of water, and titrate with 0.1 *N* sodium thiosulfate, adding starch T.S. as the end-point is neared. Each ml. of 0.1 *N* thiosulfate is equivalent to 5.585 mg. of Fe. Not less than 21.0% and not more than 23.0% is found.

Gallic Acid, $C_6H_2(OH)_3COOH.H_2O$—188.14—White, or nearly white, crystals, or powder. Sparingly soluble in cold water; very soluble in boiling water and in alcohol.

Distinction from tannic acid—Its cold, saturated solution neither colors nor precipitates solutions of pure ferrous salts and yields no precipitate with gelatin T.S.

Insoluble matter—Ten g., dissolved in 300 ml. of hot water, shows not more than 1 mg. of insoluble matter (0.01%).

Residue on ignition—Ignite 10 g., cool, add 1 ml. of sulfuric acid, and ignite again: the residue weighs not more than 1 mg. (0.01%).

Sulfate—Dissolve 2 g. in 50 ml. of hot water, cool in ice water while stirring, and filter. Dilute the filtrate to 50 ml., and to 25 ml. add 1 ml. of 1 *N* hydrochloric acid and 2 ml. of barium chloride T.S. Any turbidity produced in 10 minutes does not exceed that of a standard containing 50 mcg. of sulfate (SO_4), 1 ml. of 1 *N* hydrochloric acid, and 2 ml. of barium chloride T.S. (50 parts per million).

Hematein, $C_{16}H_{12}O_6$—300.27—Prepared from logwood extract or from hematoxylin by treatment with ammonia and exposure to air.

Description—Reddish brown crystals with a yellowish green metallic luster.

Solubility—Very slightly soluble in water (about 1 in 1700); slightly soluble in alcohol or in ether; insoluble in benzene or in chloroform; freely soluble in diluted ammonia solution to form a solution of dusky purplish red color and in an aqueous solution of sodium hydroxide (1 in 50) to form a solution of bright red color, viewed in each case through a layer 1 cm. deep.

Melting range, page 814—Melts at a temperature above 200° and tends to decompose at 250°.

***n*-Heptane,** $CH_3(CH_2)_5CH_3$—100.21—A clear, colorless, volatile, flammable liquid consisting essentially of C_7H_{16}. It has a characteristic odor. Practically insoluble in water; soluble in absolute alcohol; miscible with ether, with chloroform, with benzene, and with most fixed and volatile oils.

Boiling range, Method II, page 782—It distils completely between 85° and 100°.

Residue on evaporation—Evaporate 100 ml. to dryness on a steam bath and dry at 105° for 30 minutes: the weight of the residue does not exceed 1 mg. (10 parts per million).

Oils and fats—Pour 10 ml. in portions upon clean, odorless filter paper: there is no disagreeable color and no greasy stain is visible on the paper after standing 30 minutes.

Hydrobromic Acid, 48 Percent, HBr—80.91—Clear, colorless or faintly yellow liquid. On prolonged exposure to air it develops a yellow color. Miscible with water or ethanol. The specific gravity is about 1.5. *Keep protected from light.*

Assay—Tare a glass-stoppered conical flask containing about 15 ml. of water. Quickly add about 4 ml. of the acid and weigh. Dilute with water to 50 ml. and titrate with 1 *N* sodium hydroxide, using phenolphthalein indicator. Each ml. of 1 *N* sodium hydroxide corresponds to 80.91 mg. of HBr. Not less than 47.0% and not more than 49.0% is found.

Organic substances—Dilute 25 ml. with 25 ml. of water in a glass-stoppered cylinder, shake well, and note the odor. No foreign odor should be observed.

Residue on ignition—To 34 ml. (50 g.) in a tared dish (not platinum) add 0.05 ml. of sulfuric acid, evaporate as far as possible on the steam bath, then heat gently to volatilize the solution. Finally, ignite at 800 ± 25° for 15 minutes. The weight of the residue should not exceed 1 mg. (20 parts per million).

Chloride—To 0.67 ml. (1 g.) in a 150-ml. (conical) flask add 50 ml. of dilute nitric acid (1 in 4) and digest on the steam bath until the solution is colorless. Wash down the sides of the flask with a little water and digest for an additional 15 minutes. Cool, filter if necessary through a chloride-free filter, and dilute with water to 100 ml. Dilute a 2-ml. portion to 23 ml. Prepare a standard containing 0.01 mg. of chloride ion (Cl) in 23 ml. of water. Add 1 ml. of nitric acid and 1 ml. of silver nitrate T.S. to each. Any turbidity produced in the solution of the sample should not exceed that in the standard (0.05%).

Iodide—Dilute 4 ml. (6 g.) with 20 ml. of water. Add 5 ml. of chloroform, 0.2 ml. of ferric chloride T.S., and 0.1 ml. of dilute sulfuric acid (1 in 16) and mix gently in a separator. Draw off the chloroform layer into a comparison tube of about 1.5-cm. diameter. No violet color should be observed on looking down through the chloroform (about 30 parts per million).

Sulfate and sulfite (*as* SO_4)—Dilute 4.0 ml. (6 g.) to 60 ml. with water. To 20 ml. of the solution add a slight excess of bromine water and boil to expel the excess bromine. Add 10 to 20 mg. of sodium carbonate and evaporate to dryness on the steam bath. Dissolve the residue in 4 ml. of water plus 1 ml. of dilute hydrochloric acid (1 in 20), filter if necessary through a small filter, wash with two 2-ml. portions of water, and dilute with water to 10 ml. Add 1 ml. of barium chloride T.S. Any turbidity should not exceed that produced by 0.06 mg. of sulfate ion (SO_4) in an equal volume of solution containing the quantities of reagents used in the test. Compare 10 minutes after adding the barium chloride to the sample and standard solutions (30 parts per million).

Heavy Metals—To 2.7 ml. (4 g.) in a beaker add about 10 mg. of sodium carbonate and evaporate to dryness on the steam bath. Dissolve the residue in 25 ml. of water: the heavy metals limit is 5 parts per million.

Iron—To 6.6 ml. (10 g.) add about 10 mg. of sodium carbonate and evaporate to dryness on the steam bath. Dissolve the residue in 2 ml. of hydrochloric acid, dilute with water to 50 ml., and add 30 to 50 mg. of ammonium persulfate crystals and 3 ml. of ammonium thiocyanate solution (3 in 10). Any red color should not exceed that produced by 0.01 mg. of iron (Fe) in an equal volume of solution containing the quantities of reagents used in the test (1 part per million).

Selenium—Place 100 ml. (150 g.) in an all-glass distilling apparatus, add 2 ml. of bromine, and distil off approximately 25 ml. Dilute the distillate with an equal volume of water and decolorize with sulfurous acid. Add 0.1 g. of hydroxylamine hydrochloride and warm gently on the steam bath for 30 minutes. Cool to room temperature, filter through a white asbestos pad in a small porcelain filter crucible, without washing, and examine immediately. No pink or red color should be observed on the asbestos pad (about 1 part per 10,000).

Hydroquinone (*p-Dihydroxybenzene*), $C_6H_6O_2$—110.11—Colorless or white crystals. Darkens in air and light. Soluble in 15 parts of water; freely soluble in alcohol and in ether. Its solutions become brown if exposed to air, the rate of oxidation becoming more rapid in the presence of alkalies. *Keep in well-closed containers protected from light.*

Melting range, page 814—Between 172° and 174°.

Residue on ignition—Ignite 2 g. with 1 ml. of sulfuric acid: the residue does not exceed 1 mg. (0.05%).

8-Hydroxyquinoline (*Oxine*), $HO.C_9H_6N$—145.16—White crystals or a white, crystalline powder. Insoluble in water; soluble in alcohol and in diluted acids.

Melting range, page 814—Between 72.5° and 74°.

Insoluble in alcohol—Dissolve 3 g. in 40 ml. of alcohol, filter through a tared filtering crucible, wash with alcohol, dry at 105° for 1 hour, and weigh: the weight of the insoluble residue does not exceed 1.5 mg. (0.05%).

Residue on ignition—Ignite 2 g.: the weight of the residue does not exceed 1 mg. (0.05%).

Sulfate—Dissolve 1 g. in 1 ml. of hydrochloric acid and dilute with 20 ml. of water. Heat to boiling and add 1 ml. of barium chloride T.S. No turbidity is observed after standing for 30 minutes (about 0.02% SO_4).

Suitability for magnesium determinations—Dissolve 500 mg. of magnesium chloride ($MgCl_2.6H_2O$) in 20 ml. of water containing 2 ml. of diluted hydrochloric acid, and add water to make 100 ml. Dilute 10 ml. of the solution to 50 ml. and add 3.5 ml. of a solution of the 8-hydroxyquinoline, prepared by dissolving 2.5 g. in 5 ml. of warm glacial acetic acid and pouring into 95 ml. of water at 60°. Heat to 80°, add, with stirring, 2 ml. of ammonia T.S., allow to cool for 10 minutes, and filter. The filtrate is yellow and alkaline, and yields a yellow precipitate when 5 ml. of the magnesium chloride solution is added to it and the mixture warmed.

Iodic Acid, HIO_3—175.91—Slightly yellow crystals or crystalline powder. It is soluble in about 0.5 part of water, and somewhat soluble in alcohol of 87% or less concentration. At about 170° it decomposes into I_2O_5 and water.

Residue on ignition—Ignite 10 g. in a porcelain crucible, cool, and weigh. The weight of the residue does not exceed 5 mg. (0.05%).

Chloride and bromide—Mix 1 g. of the powdered sample with 300 mg. of powdered potassium hydroxide and add 2 g. of pure sucrose. Thoroughly mix and ignite at a low temperature in a porcelain crucible in small portions, by making small additions of the materials to the crucible when the reaction has subsided. Treat the residue with 10 ml. of hot water and 1 ml. of nitric acid, filter, and wash with 10 ml. of hot water. Cool, and add 5 ml. of ammonia T.S. Add 20 ml. of 5% silver nitrate solution with constant stirring, dilute to 50 ml., and filter. To 25 ml. of the filtrate add a slight excess of nitric acid. The turbidity should not be greater than that produced by 100 mcg. of chloride ion in the same volume of solution made with the same quantities of the same reagents used in the test (0.02%).

Iodide—Dissolve 1 g. in 20 ml. of water, and add 1 ml. of chloroform and 0.5 ml. of 1 *N* sulfuric acid: no violet color is produced in the chloroform in 1 minute.

Sulfate—Add 100 mg. of sodium carbonate to 5 g. of the sample and evaporate to dryness with 20 ml. of hydrochloric acid and repeat twice using 10 ml. of acid each time. Dissolve the residue in 50 ml. of water, add 1 ml. of dilute hydrochloric acid (1:3), filter, heat to boiling, add 5 ml. of barium chloride T.S., and allow to stand overnight. Any turbidity should not be greater than that produced by 500 mcg. of sulfate ion in a solution of the same volume and containing the same quantities of the same reagents used in the test (0.01%).

Heavy metals—Dissolve 2 g. and 100 mg. of sodium carbonate in 10 ml. of hydrochloric acid and evaporate to dryness. Successively add 5-ml. portions of hydrochloric acid and evaporate to dryness after each addition. Dissolve the residue in 20 ml. of water, neutralize with ammonia T.S., add 1 ml. of 0.1 *N* hydrochloric acid, and pass hydrogen sulfide through the solution. Any darkening should not exceed that produced in a blank containing 20 mcg. of Pb (10 parts per million).

Iron—Add ammonia T.S. to the solution obtained in the test for *Heavy metals* until it is alkaline. Any green color observed should not be greater than that produced in a blank containing 20 mcg. of Fe (10 parts per million).

Ion-exchange Resin*—An intimate mixture of 4 parts of a strongly acidic cation exchanger in the hydrogen form (produced by sulfonation of a styrene-divinylbenzene copolymer, representing 8 to 10% divinylbenzene) and 6 parts of a strongly basic anion exchanger in the hydroxyl form (produced by amination with trimethylamine of a chloro-methylated styrene-divinylbenzene copolymer, representing 3 to 5% divinylbenzene).

Iron, Reduced, Fe—55.85—A gray, fine powder. Insoluble in water; soluble in dilute acids. It oxidizes on exposure to air and moisture. *Keep in well-closed containers.*

Assay—Weigh accurately about 200 mg. and transfer it to a 300-ml. conical flask. Add 50 ml. of diluted sulfuric acid and close the flask with a stopper containing a valve, made by inserting a glass tube connected to a short piece of rubber tubing with a slit on the side and a glass rod inserted in the other end, arranged so that gases can escape, but air cannot enter. Heat on a steam bath until the iron is dissolved. Cool the solution, dilute with 50 ml. of freshly boiled and cooled water, add 2 drops of orthophenanthroline T.S. and titrate with 0.1 *N* ceric sulfate, until the red color is changed to weak blue. Each ml. of 0.1 *N* ceric sulfate is equivalent to 5.585 mg. of Fe: not less than 93% is found.

Sulfuric acid-insoluble—To 1 g. add 25 ml. of diluted sulfuric acid and warm on a steam bath until the evolution of hydrogen ceases. Collect any undissolved residue on a filter, wash it with 2% sulfuric acid, then with water, and dry at 105°: the weight of the residue does not exceed 5 mg. (0.5%).

Nitrogen—Add in small portions 1.5 g. to a mixture of 2 ml. of sulfuric acid and 30 ml. of water contained in a distilling flask. Cool, add 20 ml. of water and 50 ml. of sodium hydroxide solution (3 in 10), and slowly distil about 40 ml. into 5 ml. of water containing 1 drop of diluted hydrochloric acid. To the distillate add 2 ml. of sodium hydroxide T.S. and 2 ml. of alkaline mercuric potassium iodide T.S.: any color produced is not darker than that obtained by treating 120 mcg. of ammonium chloride (30 mcg. N) and 500 mg. of the sample in the same manner (30 parts per million).

Sulfide—To 1 g. contained in a 150-ml. flask, add 20 ml. of diluted sulfuric acid: the gas evolved does not darken moistened lead acetate paper within 2 minutes.

Isoniazid (*Isonicotinic Acid Hydrazide*)—Use *Isoniazid*, USP.

Isonicotinic Acid Hydrazide (*Isoniazid*)—See *Isoniazid.*

Isopropyl Acetate, $C_5H_{10}O_2$—102.13—A colorless liquid, containing not more than 0.5% alcohol as isopropyl alcohol. Neutral to indicator paper. Slightly soluble in water; miscible with alcohol and with ether. Specific gravity about 0.875.

Boiling range—Between 86° and 88°.

Refractive index (at 20°), page 858—1.3775 ± 0.0005.

Lead Dioxide, PbO_2—239.19—A dark brown powder. Insoluble in water, in alcohol, and in nitric acid. It is decomposed by hydrochloric acid with the evolution of chlorine. It is dissolved by concentrated solutions of alkali hydroxides.

Assay—Weigh accurately about 500 mg., add 50.0 ml. of 0.1 *N* potassium arsenite, 10 ml. of 1% potassium bromide, and 25 ml. of dilute hydrochloric acid (2 in 3). Stir and crush the lead dioxide and heat to about 50° to hasten complete solution and reaction. Cool and titrate the excess potassium arsenite with 0.1 *N* potassium bromate. The end-point may be detected either with methyl orange T.S. or potentiometrically. Each ml. of 0.1 *N* potassium arsenite is equivalent to 11.96 mg. of PbO_2. Not less than 95% is found.

Acid-insoluble matter—To 1 g. add 25 ml. of water and 3 ml. of nitric acid. Add carefully with stirring 5 ml. of 30% hydrogen peroxide or more, if needed, to dissolve all the lead dioxide. Filter through a tared filtering crucible, wash thoroughly, and dry at 105°. The weight of the residue does not exceed 2 mg. (0.2%). Reserve the filtrate for the test for *Substances not precipitated by hydrogen sulfide.*

Carbon compounds—Ignite 2 g. in a combustion tube at 500° to 600° for 30 minutes in a current of air (or oxygen) free of carbon dioxide. Pass the evolved gases into a solution containing 20 ml. of dilute ammonium hydroxide reagent solution (2.5% NH_3) and 2 ml. of water. Prepare a standard by adding 0.10 mg. of carbon as carbonate (1.7 ml. of 0.01 *N* sodium carbonate) to 20 ml. of the same ammonium hydroxide reagent solution. Add 2 ml. of barium chloride T.S. to each and compare promptly. The turbidity in the solution representing the sample does not exceed that in the standard (50 parts per million).

Chloride—Dissolve 2 g. in 20 ml. of water, and add 2 ml. of glacial acetic acid, and 2 ml. of 30% hydrogen peroxide. Filter and dilute to 100 ml. To 25 ml. add 1 ml. of nitric acid and 1 ml. of silver nitrate T.S. Any turbidity does not exceed that produced by 10 mcg. of chloride ion in an equal volume of solution containing the quantities of reagents used in the test (20 parts per million).

Nitrate—Dissolve 1 g. in a solution of

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* A suitable resin is that known as "Amberlite MB-1," produced by Rohm & Haas Co., Philadelphia, PA.

10 ml. of water, 1 ml. of acetic acid, and 0.5 ml. of 30% hydrogen peroxide. Pass sulfur dioxide through the solution to precipitate the lead, filter and wash with a few ml. of water. Add 5 mg. of sodium chloride to the filtrate, heat to boiling, and digest in an uncovered beaker on a steam bath for 15 minutes. Cool, and adjust the volume to 10 ml. Add 0.2 ml. of indigo carmine T.S. and 10 ml. of sulfuric acid. The blue color is not completely discharged in 5 minutes (50 parts per million).

Sulfate—Decompose 2 g. with 10 ml. of hydrochloric acid and 3 ml. of nitric acid and evaporate to dryness on a steam bath. Add 25 ml. of water and 2 g. of sodium carbonate and digest on a steam bath for several hours, with occasional stirring. Dilute to 100 ml. and filter. Neutralize the filtrate with hydrochloric acid and add an excess of 1 ml. of the acid. Heat to boiling, add 5 ml. of barium chloride T.S., digest on a steam bath for 2 hours, and allow to stand overnight. Filter, wash thoroughly, and ignite. The weight of the ignited precipitate is not more than 2.5 mg. greater than the weight obtained in a blank test (0.05%).

Manganese—Decompose 5 g. with 15 ml. of hydrochloric acid. Add 10 ml. of sulfuric acid and evaporate to fumes. Cool and cautiously add 20 ml. of water. Add 500 mg. of lead dioxide, heat on a steam bath for 5 minutes, dilute to 50 ml., and filter through a filtering crucible. Any color does not exceed that produced when a solution of a manganese salt containing 10 mcg. of manganese is treated exactly like the sample (2 parts per million).

Other hydrogen sulfide metals—Dissolve 500 mg. in 5 ml. of nitric acid and 5 ml. of hydrogen peroxide T.S. Add 5 ml. of sulfuric acid and evaporate to fumes. Cool, cautiously dilute to 40 ml., and allow to stand until the solution is cool and the precipitate has settled. Filter, do not wash, add 10 ml. of sulfurous acid to the filtrate and boil until the odor of sulfur dioxide disappears. Cool, dilute to 50 ml., and pass hydrogen sulfide through the solution. No red color is produced and any darkening does not exceed that produced by 100 mcg. of lead in an equal volume of solution containing the quantities of reagents used in the test (about 0.05% as Cu).

Substances not precipitated by hydrogen sulfide—Evaporate to dryness the filtrate obtained in the test for *Acid-insoluble matter*. Moisten the residue with 0.2 ml. of hydrochloric acid, dissolve in 100 ml. of water, and pass in hydrogen sulfide until the lead is completely precipitated. Filter, but do not wash. Evaporate 50 ml. of the clear filtrate to dryness in a tared dish. Heat gently to volatilize the excess salts and acids, and finally ignite at 800 ± 25° for 15 minutes. The weight of the ignited residue is not more than 2.5 mg. (0.5%).

Lithium Oxalate, $Li_2C_2O_4$—101.90—A white crystalline powder, soluble in about 17 parts of water. It is insoluble in alcohol.

Assay—Weigh accurately about 1 g., previously dried to constant weight at 105°, dissolve in water, and dilute to 200.0 ml. Dilute 25.0 ml. of the resulting solution with 75 ml. of water, add 3 ml. of sulfuric acid, and then add slowly 20 ml. of 0.1 *N* potassium permanganate. Heat to 70°, and complete the titration with the permanganate until a pale pink color persists for 15 seconds. One ml. of 0.1 *N* permanganate equals 5.095 mg. of $Li_2C_2O_4$. It contains not less than 99% of $Li_2C_2O_4$.

Neutrality—Aqueous solutions are faintly alkaline to litmus but are not reddened by 1 drop of phenolphthalein T.S.

Chloride—Ignite 2 g., and to the residue add 20 ml. of water. Neutralize the solution with nitric acid, and add 0.5 ml. excess of the acid. Filter, and add to the filtrate 1 ml. of silver nitrate T.S. Any turbidity produced is not greater than that produced in a blank to which 40 mcg. of chloride has been added.

Sulfate—Ignite 2 g. in a porcelain crucible protected from sulfur in the flame. Boil the residue with 20 ml. of water and 2 ml. of bromine T.S., then add 5 ml. of hydrochloric acid and evaporate to dryness on a water bath. Dissolve the residue in 20 ml. of water and 1 ml. of 1 *N* hydrochloric acid, filter, and add to the filtrate 2 ml. of barium chloride T.S. Any resulting turbidity is not greater than that in a control made as follows: evaporate 2 ml. of bromine T.S. and 5 ml. of hydrochloric acid to dryness on a water bath, dissolve the residue and 0.3 mg. of SO_4 in sufficient water to make 20 ml., then add 1 ml. of 1 *N* hydrochloric acid and 2 ml. of barium chloride T.S.

Heavy metals—Ignite 4 g. gently in a porcelain crucible. Add to the residue 5 ml. of water, 5 ml. of hydrochloric acid, and 2 ml. of nitric acid, and evaporate to dryness on a water bath. Dissolve the residue in 40 ml. of water, and filter. To 10 ml. of the filtrate add 40 mcg. of lead, as $Pb(C_2H_3O_2)_2$, dilute with water to 30 ml., and add 1 ml. of 1 *N* acetic acid (A). To the remaining 30 ml. of the filtrate add 1 ml. of 1 *N* acetic acid (B). Then to each add 10 ml. of hydrogen sulfide T.S.: B is no darker than A.

Sodium—Ignite 1 g. in a platinum crucible and dissolve the residue in 10 ml. of diluted hydrochloric acid, and filter. The solution tested on a platinum wire in the full-heat flame of a Bunsen burner imparts no distinct yellow color and only a fleeting orange tinge to the red lithium flame (less than 0.05% sodium oxalate).

Potassium—Ignite 5 g. of the salt to carbonate in a platinum crucible, dissolve it in a small amount of water, neutralize the solution with hydrochloric acid, and filter. Evaporate this solution to dryness on a water bath and redissolve the residue in 15 ml. of water. Add 5 ml. of sodium cobaltinitrite T.S. and allow to stand overnight. Any precipitate formed should not be greater than that produced by an amount of potassium chloride equivalent to 500 mcg. of K, dissolved in 15 ml. of water and treated with 5 ml. of the same sodium cobaltinitrite T.S. as used in the test, and allowed to stand overnight (0.01% of K).

Magnesium Silicate, Chromatographic—An extremely white, hard, powdered (60–100 mesh) magnesia–silica gel. Suitable for use as an adsorbent in column chromatography.*

Maleic Acid, $C_4H_4O_4$—116.07—A white, odorless, crystalline powder. Soluble in 1.5 parts of water, in 2 parts of alcohol and in 12 parts of ether.

Assay—Dissolve about 2 g., accurately weighed, in 100 ml. of water and titrate with 1 *N* sodium hydroxide, using phenolphthalein T.S. as the indicator. Each ml. of 1 *N* sodium hydroxide is equivalent to 58.04 mg. of $C_4H_4O_4$. It contains not less than 99% of $C_4H_4O_4$ calculated on the dried basis.

Loss on drying—It loses not more than 1.5% when dried over P_2O_5 at not more than 5 mm. of Hg for 2 hours.

Residue on ignition—Not more than 0.1%.

Malt Extract—Obtained by extracting malt with water and then concentrating or drying. A sweet, viscous, light brown liquid or a powder. It dissolves partially in cold water, but readily in warm water. For use in the preparation of *Malt, Agar Medium,* it must contain no glycerin. It is capable of converting not less than 5 times its weight of starch into water-soluble sugars.

Assay—Determine the percentage of moisture in potato starch by drying about 500 mg., accurately weighed, at 120° for 4 hours. Thoroughly mix a quantity equivalent to 5 g. of dried starch, in a beaker, with 10 ml. of cold water. Add 140 ml. of boiling water, and heat on a steam bath, with constant stirring, for 2 minutes or until a translucent, uniform paste is obtained. Cool to 40° in a suitable bath previously adjusted to this temperature. Add 20 ml. of a fresh solution prepared by dissolving 5 g. of Malt Extract in sufficient water to make 100 ml. of solution at 40°. Mix this well, and maintain the same temperature for 30.0 minutes, stirring frequently. A thin, clear liquid is produced. Stir, and add at once 0.1 ml. of this liquid to a previously made mixture of 0.2 ml. of 0.1 *N* iodine and 60 ml. of water: no blue or reddish color develops.

Solubility and heat stability—Dissolve 3 g. in 100 ml. of water: the solution is clear and remains so upon standing. Heat a portion of the solution in an autoclave at 121° for 20 minutes: the solution remains clear.

Loss on drying—Dry it at 105° for 1 hour: it loses not more than 5% of its weight.

Methyl Acetate, $C_3H_6O_2$—74.08—A colorless liquid, having a characteristic odor. Soluble in water; miscible with alcohol and with ether. The specific gravity is about 0.933.

Refractive index, page 858—Between 1.3615 and 1.3625 at 20°.

Boiling range—Not less than 95% distils between 57° and 58°.

Methyl Ethyl Ketone, C_4H_8O—72.11—A colorless liquid having an acetone-like odor. Soluble in water; miscible with alcohol, with ether, and with benzene.

Specific gravity, page 866—Between 0.801 and 0.803.

Nonvolatile residue—Allow 50 ml. to evaporate spontaneously and dry the residue at 105° for 1 hour: the residue weighs not more than 1 mg. (20 parts per million).

Boiling range—Between 79.0° and 81.0°.

Acidity—Add 25 ml. to 10 ml. of 80% alcohol previously neutralized with 0.02 *N* sodium hydroxide to the production of a pink color with phenolphthalein T.S. Titrate with 0.02 *N* sodium hydroxide to the production of a pink color: not more than 0.5 ml. of 0.02 *N* sodium hydroxide is required (30 parts per million as $C_2H_4O_2$).

Methyl Iodide, CH_3I—141.94—A clear liquid, colorless when freshly distilled, but on exposure to air and light becomes brown through liberation of iodine which may be removed by shaking with a globule of mercury or with silver leaf. Slightly soluble in water. Miscible with alcohol, with ether, and with solvent hexane.

Boiling range—Distil 100 ml.: the difference between the temperatures observed when 1 ml. and 95 ml. have distilled is not more than 1°. Its boiling temperature at 760 mm. of Hg pressure is 42.4°.

Specific gravity, page 866—The specific gravity is between 2.270 and 2.285.

Nonvolatile matter—Evaporate 4 ml. to dryness on a steam bath and dry the residue at 105° for 1 hour: the residue weighs not more than 1 mg. (0.01%).

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* A suitable grade of chromatographic magnesium silicate is "Florisil, 60–100 mesh" available from Floridin Company, 3 Penn Center, Pittsburgh, PA 15235.

to separate, and drain the alcohol layer into a clean, dry comparison tube: any red color in the alcohol extract is not darker than that from a control containing 20 mcg. of added Fe (20 parts per million).

Lead—Dissolve 2 g. in 30 ml. of water, and add 1 ml. of acetic acid and 1 ml. of potassium chromate solution (1 in 10): any turbidity produced does not exceed that of a control containing 100 mcg. of added Pb (50 parts per million).

Substances not precipitated by ammonium sulfide—Dissolve 2 g. in 100 ml. of dilute stronger ammonia water (5 in 100), saturate the solution with hydrogen sulfide, and filter. Evaporate 50 ml. of the clear filtrate to a small volume, filter again if necessary, evaporate to dryness, and ignite at 800 ± 25° for 15 minutes: the residue weighs not more than 2.0 mg. (0.20%).

Sulfate—Dissolve 10 g. in 150 ml. of water, add 1 ml. of hydrochloric acid, filter, and heat the filtrate to boiling. Add 10 ml. of barium chloride T.S., and let stand overnight. If any precipitate is formed, filter, wash, ignite, and weigh: the residue weighs not more than 1.2 mg. (50 parts per million).

Nile Blue Hydrochloride (*5-Amino-9-diethylaminobenzo*[a]*phenazoxonium chloride*) — $C_{20}H_{20}ClN_3O$ — 353.85 — Slightly soluble in alcohol and in glacial acetic acid. Transition interval: from pH 9.0 to 13.0. Color change: from blue to pink.

*Absorption characteristics**—Dissolve 50 mg. of Nile Blue Hydrochloride in 125 ml. of 95% alcohol and then dilute to 250 ml. with water. Dilute 3 ml. of this solution to 200 ml. with 50% alcohol. Determine the absorbance in a suitable spectrophotometer in a 1-cm. cell. The absorbance maximum is in the range 635–646 mμ; ratio P − 15/P + 15 is from 1.02 to 1.16, where P is the wavelength of maximum absorbance.

***o*-Nitroaniline,** $C_6H_6N_2O_2$—138.13—Orange-yellow crystals. Slightly soluble in cold water; soluble in hot water; freely soluble in alcohol and in chloroform. It forms water-soluble salts with mineral acids.

Melting range, page 814—Between 71° and 72°.

***m*-Nitrobenzaldehyde,** $NO_2C_6H_4CHO$—151.12—A yellow, crystalline powder. Insoluble in water; soluble in alcohol, in chloroform and in ether.

Melting range, page 814—Between 57° and 59°.

***o*-Nitrobenzaldehyde,** $NO_2C_6H_4CHO$—151.12—Pale yellow or light greenish yellow needles having a benzaldehyde-like odor. Soluble in alcohol, in benzene and in ether; practically insoluble in water.

Melting range, page 814—Between 42° and 44°.

Solubility in alcohol—One g. dissolves practically completely in 20 ml. of alcohol, giving a clear, pale yellow or greenish yellow solution.

Residue on ignition—It yields not more than 0.1% of residue on ignition.

Nitromethane, CH_3NO_2—61.04—An oily liquid. Soluble in water, alcohol, ether, and dimethylformamide. Specific gravity is about 1.132. Water solutions are acid to litmus.

Refractive index, page 858—About 1.380 at 22°.

Boiling range—Between 101° and 103°.

Residue on evaporation—The residue from 50 ml. is negligible.

1 - Nitroso - 2 - naphthol, $C_{10}H_7NO_2$—173.17—A dark brown powder. Slightly soluble in water and in alcohol.

Melting range, page 814—Between 103° and 105°.

Nonylphenoxypoly(ethyleneoxy)ethanol—A clear, viscous, pale yellow liquid with an aromatic odor. May exhibit slight solidification on cooling; warming with agitation will restore to original condition. Density: about 1.06. Soluble in alcohol, in xylene, and in water. Suitable for use in gas-liquid chromatography.**

3,3′-Oxydipropionitrile, $O(CH_2CH_2CN)_2$—124.14—A clear, colorless to slightly yellow liquid. Refractive index, n_D^{20}, about 1.446.

Boiling range—Between 174° and 176° at 10 mm. Hg.

Palladous Chloride, $PdCl_2$—177.31—Dark brown, hygroscopic, crystalline powder. With water it forms a basic insoluble salt; easily soluble in dilute hydrochloric acid.

Assay—Dissolve 80 mg., accurately weighed, in 10 ml. of diluted hydrochloric acid, dilute with water to 50 ml. and add 25 ml. of dimethylglyoxime solution in alcohol (1 in 100). Allow to stand for 1 hour and filter. Check for complete precipitation with the dimethylglyoxime solution. Ignite the precipitate in a tared platinum crucible at 850° for 2 hours, cool, and weigh the palladium. The weight of the residue is not less than 59.0% of the weight of the sample.

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* From H. J. Conn "Biological Stains, 7th Edition," page 292, Williams and Wilkins, Baltimore, MD, 1961. Color Index No. 51180.

** A suitable grade of nonylphenoxypoly(ethyleneoxy) ethanol is "Igepal CO 710" available from General Aniline and Film Corporation, 140 West 51st Street, New York, NY 10020.

Paraformaldehyde, $(CH_2O)_n$—A fine, white powder having the characteristic odor of formaldehyde.

Assay—Transfer about 1 g., accurately weighed, to a 250-ml. conical flask containing 50.0 ml. of 1 *N* sodium hydroxide, and mix by swirling. Immediately, and slowly, add 50 ml. of hydrogen peroxide T.S., previously neutralized to bromothymol blue, through a small funnel placed in the neck of the flask. After the reaction moderates, rinse the funnel and inner wall of the flask with water, allow the solution to stand for 30 minutes, add bromothymol blue T.S., and titrate the excess alkali with 1 *N* sulfuric acid. Each ml. of 1 *N* sodium hydroxide is equivalent to 30.03 mg. of HCHO. Not less than 95% is found.

Residue on ignition—Not more than 0.1%.

Solubility in ammonia—Dissolve 5 g. in 50 ml. of ammonia T.S.: a practically clear, colorless solution results.

Reaction—Shake 1 g. with 20 ml. of water for about 1 minute, and filter: the filtrate is neutral to litmus paper.

Phenolphthalein, $C_{20}H_{14}O_4$—318.33—Use *Phenolphthalein*, page 543. Transition interval: from pH 8.3 to 10. Color change: from colorless to red.

Phenyl Isocyanate, C_6H_5NCO—119.12—Clear, colorless to straw-yellow liquid of medium volatility.

Caution: Phenyl Isocyanate is a violent lachrymator and the vapor is highly toxic. Handle with care.

Assay—Transfer 250 mg., accurately weighed, to a 250-ml. glass-stoppered flask. Care should be exercised to avoid loss by volatilization and avoid breathing of the vapor. Add 20 ml. of butylamine solution (25 g. of butylamine diluted to 1 liter with dioxane previously dried over potassium hydroxide pellets), stopper the flask and allow to stand for 15 minutes. Add a few drops of methyl red T.S., 25 ml. of water and titrate the excess amine with 0.1 *N* sulfuric acid. Perform a blank titration on 20 ml. of the butylamine solution (see *Residual Titrations*, page 883). Subtract the volume of 0.1 *N* sulfuric acid consumed in the sample titration from that consumed in the blank titration. Each ml. of 0.1 *N* sulfuric acid, representing this difference, is equivalent to 11.91 mg. of C_6H_5NCO. Not less than 97.0% C_6H_5NCO is found.

Phenylmercuric Nitrate—Use *Phenylmercuric Nitrate*, page 550.

Phthalic Anhydride, $C_8H_4O_3$—148.12—White chips or flakes. One g. dissolves completely in 20 ml. of methanol. Slightly soluble in water; more soluble in hot water, forming phthalic acid.

Assay—Dissolve about 2.5 g., accurately weighed, in 50.0 ml. of 1 *N* sodium hydroxide, and titrate the excess alkali with 1 *N* sulfuric acid, using phenolphthalein T.S. Each ml. of 1 *N* sodium hydroxide is equivalent to 74.06 mg. $C_8H_4O_3$. It contains not less than 99% $C_8H_4O_3$.

Melting range, page 814—Between 131° and 132°.

Piperidine, $C_5H_{11}N$—85.15—A colorless liquid. Miscible with water and with alcohol. The specific gravity is about 0.860.

Congealing range, page 794—Between 15° and 12°.

Boiling range—Not less than 95% distils between 104° and 106°.

Refractive index—About 1.454.

Polyethylene Glycol 20,000—Molecular weight range: 15,000–20,000. Hard; white, waxy solid, usually supplied in flake form. Soluble in water with subsequent gel formation.

Viscosity of 25 percent solution, page 889—Add 50.00 g. of sample to a 250-ml. widemouth screw-cap jar containing 150.0 g. of water. Attach the cap securely to the jar and roll on a mechanical roller until the sample is completely dissolved. Two to 4 hours will be required. Allow the solution to stand until all air bubbles have disappeared. Another 2 to 4 hours may be required. Adjust the temperature of the solution to 37.8 ± 0.1° and determine the kinematic viscosity on a suitable viscometer of the Ubbelohde type. The viscosity is not less than 100 centistokes.

pH, page 824—Between 6.5 and 8.0 in a solution (1 in 20). *Note:* A 5-fold dilution of the sample solution prepared for the *Viscosity of 25 percent solution* test may be used.

Residue on ignition—Not more than 0.7 percent, the use of sulfuric acid being omitted.

Polyvinyl Alcohol*—$(C_2H_4O)_n$—A white powder. Soluble in water; insoluble in organic solvents.

pH, page 824—Prepare a 1 in 25 solution, and determine its pH: the pH is between 5.0 and 8.0.

Loss on drying—It loses not more than 5% of its weight when dried at 110° to constant weight.

Residue on ignition—It yields not more than 0.75% of residue on ignition.

Potassium Cyanate, KOCN—81.12—Colorless crystals or crystalline powder.

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* Suitable grades of polyvinyl alcohol are available from J. T. Baker Chemical Co. (Catalog No. U 232), Phillipsburg, NJ 08865, or from E. I. du Pont de Nemours and Co. (Elvanol 51-05), Wilmington, DE 19898.

Soluble in water; very slightly soluble in alcohol.

Caution: On account of the extremely poisonous nature of this reagent and of the gas evolved on treatment with acid, all tests must be made in a hood with a strong draft and special care must be taken to avoid inhaling the fumes. Pipets must not be used in measuring its solutions.

Insoluble matter—Dissolve 20 g. in 150 ml. of water and allow to stand on the steam bath for 1 hour. Filter through a tared sintered-glass crucible (retain the filtrate), wash thoroughly with hot water, dry at 105° for 1 hour, cool, and weigh. The weight of the insoluble residue does not exceed 1 mg. (50 parts per million).

Solution A—Dilute the filtrate from the test for *Insoluble matter* to a volume of 200 ml. with water.

Chloride—Transfer 10 ml. (1 g.) of *Solution A* to a 100-ml. volumetric flask, add 20 ml. of water, 25 ml. of diluted sulfuric acid and evaporate to half the original volume. Replace the water lost and re-evaporate to half the original volume. Cool, filter, dilute the filtrate to 50 ml. with water, and add 2 ml. of nitric acid and 1 ml. of silver nitrate T.S.: any turbidity does not exceed that produced by 50 mcg. of chloride (Cl) contained in a similarly treated control (50 parts per million).

Sulfate—To 50 ml. (5 g.) of *Solution A*, add 10 ml. of hydrochloric acid and evaporate to dryness on the steam bath. Warm the residue with 50 ml. of water, add 1 ml. of hydrochloric acid, filter if necessary, and dilute the filtrate to 100 ml. with water. Heat the solution to boiling, add 10 ml. of barium chloride T.S., digest on the steam bath for 2 hours, and allow to stand overnight. Filter, wash thoroughly, ignite in a tared platinum crucible, cool, and weigh: the weight of the ignited precipitate ($BaSO_4$) is not more than 6.1 mg. greater than the weight obtained in a blank test (0.05%).

Iron—Treat 10 ml. (1 g.) of *Solution A* with 3 ml. of hydrochloric acid and 2 ml. of 30% hydrogen peroxide in a covered beaker on the steam bath until the reaction ceases. Remove the cover and evaporate to dryness. Take up the residue with 25 ml. of water, and add 2 ml. of hydrochloric acid, 30 to 50 mg. of ammonium persulfate ($(NH_4)_2S_2O_8$) and 3 ml. of ammonium thiocyanate T.S.: any red color does not exceed that produced by 0.03 mg. of Fe contained in a similarly treated control (30 parts per million).

Potassium Hyaluronate—A white to cream-colored powder. Freely soluble in water. Store in tight containers in a refrigerator.

Inhibitor content—Prepare as directed in the *Assay* under *Hyaluronidase for Injection*, page 347, a quantity of *Standard solution* containing 1 NF Hyaluronidase Unit in each ml., and a similar quantity of acetate-buffered *Standard solution* using as the solvent 0.1 *M*, pH 6 sodium acetate buffer (prepared by diluting the 0.2 *M* buffer prepared as directed below with an equal volume of water). Prepare from the potassium hyaluronate under test 10 ml. of *Potassium hyaluronate stock solution*, and dilute 2 ml. of it with the specified *Phosphate buffer solution* to make a *Hyaluronate solution*. In the same way, and concurrently, dilute a second 2-ml. portion of the stock solution with 0.2 *M*, pH 6 sodium acetate buffer (containing 16.4 g. of anhydrous sodium acetate and 0.45 ml. of glacial acetic acid in each liter).

Place 0.5-ml. portions of the *Hyaluronate solution* in each of four 16 × 100-mm. test tubes, and 0.5-ml. portions of the acetate-buffered *Hyaluronate solution* in two similar tubes. To two of the four tubes containing *Hyaluronate solution* add 0.5 ml. of *Diluent for hyaluronidase solutions*, page 347. To the remaining two tubes, on a rigid schedule, at half-minute intervals, add 0.5 ml. of *Standard solution*. Similarly, to the two tubes containing acetate-buffered *Hyaluronate solution* add at half-minute intervals 0.5-ml. portions of acetate-buffered *Standard solution*. Then proceed as directed in the second paragraph under *Procedure*, beginning with "Mix the contents," as far as "Plot the average." The reduction in absorbance of acetate-buffered *Hyaluronate solution* is not less than 25% of that observed in the *Hyaluronate solution*.

Turbidity production—The average absorbance of the solutions in the two tubes containing *Hyaluronate solution* and *Diluent for hyaluronidase solutions* prepared in the test for *Inhibitor content* is not less than 0.26 at a wavelength of 640 mμ in a suitable spectrophotometer using a 1-cm. cell.

Potassium Oxalate, $K_2C_2O_4 . H_2O$—184.24—Colorless or white crystals; efflorescent in dry air. Freely soluble in water; slightly soluble in alcohol.

Insoluble matter—The insoluble matter from 10 g. weighs not more than 1.0 mg. (0.01%).

Neutrality—Dissolve 2 g. in 200 ml. of water, and add 10.0 ml. of 0.01 *N* oxalic acid and 0.2 ml. of a 1% solution of phenolphthalein. Boil the solution for 10 minutes while passing a stream of carbon dioxide-free air through it, and then cool the solution rapidly while continuing to pass the carbon dioxide-free air through it. Titrate with 0.01 *N* sodium hydroxide until the color matches that in a buffer solution containing, in 1 liter, 3.1 g. of boric acid, 3.8 g. of potassium chloride, 5.90 ml. of 1 *N* sodium hydroxide, and 0.2 ml. of the 1% solution of phenolphthalein. Not less than 9.2 ml. nor more than 10.5 ml. of 0.01 N sodium hydroxide is required.

Chloride—Ignite 1 g. in a platinum crucible, dissolve the residue in 20 ml. of water, neutralize the solution with nitric acid, filter, and dilute to 40 ml. To 20 ml. of this solution add 1 ml. of nitric acid and 1 ml. of silver nitrate T.S.: any turbidity does not exceed that in a control containing 0.01 mg. of added Cl (20 parts per million).

Sulfate—Mix 500 mg. with 1 ml. of water, add 1 ml. of nitric acid and 1 ml. of 30% hydrogen peroxide, and digest in a covered beaker on a steam bath until the reaction ceases. Remove the cover and evaporate to dryness. Take up the residue in 3 ml. of water and 3 ml. of hydrochloric acid, and again evaporate to dryness. Take up the residue in 1 ml. of dilute hydrochloric acid (1 in 20) and 10 ml. of water, filter if necessary, and add 1 ml. of barium chloride T.S.: any turbidity produced in 10 minutes does not exceed that produced in a control containing 50 mcg. of added SO_4 (0.01%).

Ammonium—Dissolve 1 g. in 50 ml. of ammonia-free water, and add 2 ml. of alkaline mercuric-potassium iodide T.S.: any color produced is not darker than that produced in a control containing 20 mcg. of added NH_4 (20 parts per million).

Heavy Metals—Mix 2 g. with 2 ml. of water, add 2 ml. of nitric acid and 2 ml. of 30% hydrogen peroxide, and digest in a covered beaker on a steam bath until reaction ceases. Remove the cover and evaporate to dryness. Take up the residue in 2 ml. of water and 2 ml. of nitric acid, and again evaporate to dryness. Dissolve the residue in water and dilute to 40 ml. For the control, evaporate 2 ml. of nitric acid and 1 ml. of 30% hydrogen peroxide to dryness, add 20 mcg. of Pb to the residue, and take up the residue in 10 ml. of the sample solution and 20 ml. of water. To the control and to the remaining 30 ml. of the sample solution add 1 drop of phenolphthalein T.S. and neutralize with 0.1 N sodium hydroxide. Add 1 drop of diluted acetic acid to each solution, dilute to 40 ml., and add 10 ml. of hydrogen sulfide T.S.: any brown color produced in the sample solution is not darker than that in the control (20 parts per million).

Iron—Mix 2 g. with 2 ml. of water, add 2 ml. of nitric acid and 2 ml. of 30% hydrogen peroxide, and digest in a covered beaker on a steam bath until reaction ceases. Remove the cover and evaporate to dryness. Add 5 ml. of hydrochloric acid and again evaporate to dryness. Take up the residue in water and 4 ml. of hydrochloric acid, and dilute to 100 ml.: the iron in 50 ml. of this solution corresponds to not more than 10 mcg. of Fe (10 parts per million).

Sodium (see *Sodium in reagents* under *Flame Photometry for Reagents*, USP XVIII)—*Sample Solution*—To 1 g. in a covered beaker add 1 ml. of nitric acid and 2 ml. of 30% hydrogen peroxide, and digest on a steam bath until reaction ceases. Add 1 ml. of 30% hydrogen peroxide, and again digest on the steam bath until the reaction ceases. Remove the cover, and evaporate to dryness. Dissolve the residue in water, and dilute to 100 ml. *Control Solution*—Treat 1 g. and 200 mcg. of added sodium ion (Na) as directed for the *Sample Solution*. The limit is 0.02%.

Substances darkened by hot sulfuric acid—In a recently ignited test tube heat 1 g. with 10 ml. of sulfuric acid until strong fumes of SO_3 are evolved. The acid when cooled is no darker than a mixture of the following composition: 0.2 ml. of cobaltous chloride C.S., 0.3 ml. of ferric chloride C.S., 0.3 ml. of cupric sulfate C.S., and 9.2 ml. of water.

Propylparaben—Use *Propylparaben* USP.

Pyrocatechol Violet (*Pyrocatecholsulfonphthalein*), $C_{19}H_{14}O_7S$—386.38—Reddish brown powder. Freely soluble in water; sparingly soluble in alcohol. In the pH range between 2 and 3, its solution is blue in the presence of bismuth ion and yellow in the presence of excess disodium ethylenediaminetetraacetate.

Rhodamine B (*Tetraethylrhodamine*), $C_{28}H_{31}ClN_2O_3$—479.02—Green crystals or a reddish violet powder. Very soluble in water, producing bluish red solutions which are strongly fluorescent when dilute; very soluble in alcohol; slightly soluble in dilute acids and alkali solutions. In strongly acid solution, it forms a pink complex with antimony which is soluble in isopropyl ether.

Safranin O—A dark red powder consisting of a mixture of 3,7-diamino-2,8-dimethyl-5-phenylphenazinium chloride, $C_{20}H_{19}ClN_4$—350.85, and 3,7-diamino-2,8-dimethyl-5-*o*-tolylphenazinium chloride, $C_{21}H_{21}ClN_4$—364.88. Sparingly soluble in 70% alcohol yielding a clear red solution with a yellowish red fluorescence.

Identification—

A: To 10 ml. of a 0.5% w/v solution add 5 ml. of hydrochloric acid: a bluish violet solution is produced.

B: To 10 ml. of a 0.5% w/v solution, add 5 ml. of sodium hydroxide solution; (1 in 5), a brownish red precipitate is produced.

C: To 0.1 g. add 5 ml. of sulfuric acid; a green solution is produced, which, on dilution, changes to blue and finally to red.

Absorption characteristics—Dissolve 50 mg. in 250 ml. of 50% alcohol. Dilute 3 ml. of this solution to 200 ml. with 50% alcohol. Determine the absorbance in a suitable spectrophotometer in a 1-cm. cell. The absorbance maximum is in the range 530–533 mμ; ratio P − 15/P + 15 is from 1.10 to 1.32, where P is the wavelength of maximum absorbance.*

Sawdust, Purified—It may be prepared as follows: Extract sawdust in a percolator, first with sodium hydroxide solution (1 in 100), then with dilute hydrochloric acid (1 in 100) until the acid percolate gives no test for alkaloid with mercuric potassium iodide T.S. or with iodine T.S. Then wash with water until free from acid and soluble salts, and dry. Purified sawdust meets the following test:

Alkaloids—To 5 g. of purified sawdust contained in a flask add 50 ml. of a mixture of 2 volumes of ether and 1 volume of chloroform and 10 ml. of ammonia T.S., and shake frequently during 2 hours. Decant 20 ml. of the clear, ether-chloroform liquid, and evaporate to dryness. Dissolve the residue in 2 ml. of 1 *N* hydrochloric acid and divide into 2 portions. To 1 portion add mercuric potassium iodide T.S. and to the other add iodine T.S.: no turbidity is produced in either portion.

Silica, Calcined Diatomaceous—See *Diatomaceous Silica, Calcined*, page 914.

Siliceous Earth,† Purified (*Purified Infusorial Earth; Purified Kieselgur; Terra Silicea Purificata*)—A form of silica (SiO_2) consisting of the frustules and fragments of diatoms, purified by boiling with diluted hydrochloric acid, washing, and calcining. An amorphous very fine, white, light gray or pale buff powder. It is gritty, readily absorbs moisture, and retains about four times its weight of water without becoming fluid. Insoluble in water, in acids, and in dilute solutions of the alkali hydroxides.

Loss on ignition—Weigh accurately about 1 g. and ignite to constant weight: it loses not more than 10% of its weight.

Acid-soluble substances—Digest 1 g. with 20 ml. of diluted hydrochloric acid at 50° for 15 minutes, and filter. To 10 ml. of the filtrate add 0.5 ml. of sulfuric acid, evaporate to dryness, and ignite to constant weight: the weight of the residue does not exceed 8 mg.

Carbonate—Add 1 g. to 25 ml. of diluted hydrochloric acid: no effervescence occurs.

Sulfate—Boil the mixture obtained in the test for *Carbonate* for 10 minutes, replacing any water lost by evaporation, and filter: the filtrate does not become turbid upon the addition of a few drops of barium chloride T.S.

Organic impurities—Does not darken appreciably upon ignition.

Reaction and water-soluble iron—Boil 10 g. with 50 ml. of water for 10 minutes, replace any water lost by evaporation, and filter: the filtrate is colorless and neutral to litmus paper. Add 5 drops of potassium ferrocyanide T.S. to 5 ml. of the filtrate: no blue color is produced.

Silver Diethyldithiocarbamate, $(C_2H_5)_2NCS_2Ag$—256.14—(The reagent grade product should be specified when ordered from a commercial supplier.)

The compound may be prepared as follows: Dissolve 1.7 g. of reagent grade silver nitrate in 100 ml. of water. In a separate container, dissolve 2.3 g. of sodium diethyldithiocarbamate in 100 ml. of water, and cool both solutions to 10°. Mix the two solutions, and while stirring, collect the yellow precipitate in a medium-porosity sintered-glass crucible or funnel, and wash with about 200 ml. of cold water. Dry the precipitate in vacuum at room temperature for 2 to 3 hours. The dry salt is pure yellow in color and should show no change in character after one month when stored in a light-resistant container. Discard any material which changes in color or develops a strong odor.

Silver Oxide, Ag_2O—231.74—A brownish black, heavy odorless powder. Slowly decomposes on exposure to light; absorbs carbon dioxide when moist; practically insoluble in water; freely soluble in dilute nitric acid and in ammonia; insoluble in alcohol. Store in well-closed containers; do not expose to ammonia fumes or easily oxidizable substances.

Assay—Dissolve about 500 mg., previously dried at 120° for 3 hours and accurately weighed, in a mixture of 20 ml. of water and 5 ml. of nitric acid. Dilute with 100 ml. of water, add 2 ml. of ferric ammonium sulfate T.S., and titrate with 0.1 *N* ammonium thiocyanate to a permanent reddish brown color. Each ml. of 0.1 *N* ammonium thiocyanate is equivalent to 11.59 mg. of Ag_2O. Not less than 99.7% of Ag_2O is found.

Loss on drying—Dry at 120° for 3 hours: it loses not more than 0.25% of its weight.

Nitrate—To 500 mg. add 30 mg. of sodium carbonate and 2 ml. of phenoldisulfonic acid T.S., mix well, and heat on a steam bath for 15 minutes. Cool, *cautiously* add 20 ml. of water, make alkaline with ammonia T.S., and dilute to 30 ml. with water: any color produced by the sample solution is no darker than that produced in a control containing 10 mcg. of NO_3 (20 parts per million).

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* From H. J. Conn "Biological Stains, 7th Edition," page 294, Williams and Wilkins, Baltimore, MD 1961. Color Index No. 50240.

† Suitable chromatographic grades of siliceous earth, are acid-washed "Celite 545" and "Chromosorb W," available from Johns-Manville Corp., 270 Madison Ave., New York, NY 10016; for gas chromatography, "Diatoport S" (acid- and base-washed and then silanized), is available from F and M Scientific Corp., Starr Rd. and Route 41, Avondale, PA.

Substances insoluble in nitric acid—Dissolve 5 g. in a mixture of 5 ml. of nitric acid and 10 ml. of water, dilute to about 65 ml. with water, and filter any undissolved residue on a tared filtering crucible (retain the filtrate for the test for *Substances not precipitated by hydrochloric acid*). Wash the crucible with water until the last washing shows no opalescence with 1 drop of hydrochloric acid, and dry at 105° to constant weight: the residue weighs not more than 1 mg. (0.02%).

Substances not precipitated by hydrochloric acid—Dilute the filtrate obtained in the test for *Substances insoluble in nitric acid* to 250 ml. with water, heat to boiling, and add dropwise sufficient hydrochloric acid to precipitate all of the silver (about 5 ml.), avoiding any great excess. Cool, dilute to 300 ml. with water, and let stand overnight. Filter, evaporate 200 ml. of the filtrate to dryness in a suitable tared porcelain dish, and ignite: the residue weighs not more than 1.7 mg. (0.05%).

Alkalinity—Heat 2 g. with 40 ml. of water on a steam bath for 15 minutes, cool, and dilute to 50 ml. with water. Filter, discarding the first 10 ml. of filtrate. To 25 ml. of the subsequent filtrate add 2 drops of phenolphthalein T.S., and titrate with 0.02 *N* hydrochloric acid to the disappearance of any pink color: not more than 0.2 ml. is required (0.016% as NaOH).

Soda Lime—A mixture of variable proportions of sodium hydroxide with calcium oxide or hydroxide. This reagent may or may not include an indicator. White or grayish white granules.

Loss on drying—Weigh accurately about 10 g. and dry at 200° for 18 hours: the loss in weight does not exceed 7%.

Carbon dioxide absorption capacity—To a tared Schwartz-type U-tube containing about 5 g. of anhydrous calcium chloride confined in one arm by a small plug of glass wool add 7 to 10 g. of the sample and reweigh. Connect the outlet of the U-tube to a glass tube dipping into water. Connect the inlet end through a three-way stopcock to a source of air-free carbon dioxide, dried over anhydrous calcium chloride. Connect the third arm of the stopcock to a piece of glass tubing of 5-mm. inside diameter which dips into water to a depth of 5 or 6 cm. Pass the carbon dioxide through this arm till the flow of gas is regulated at 75 to 100 bubbles a minute. Then allow the gas to pass into the U-tube which is set in a beaker of water during the period of the test. When bubbles begin to appear from the exit tube, close and disconnect the U-tube, wipe dry, and weigh: the gain in weight is not less than 25% of the weight of the sample.

Dust—Place 100 g. on a clean U. S. No. 100 standard sieve nested in a receiving pan. Cover the sieve and shake on a mechanical shaker for 5 minutes: the weight of the fine material in the receiving pan does not exceed 1.0 g. (1%).

Sodium Alizarinsulfonate (*Alizarin Red S*), $C_{14}H_7NaO_7S.H_2O$—360.28—A yellow-brown or orange-yellow powder. Freely soluble in water, producing a yellow color; sparingly soluble in alcohol.

Sensitiveness—Add 3 drops of a 1 in 100 solution to 100 ml. of water, and follow with 0.25 ml. of 0.02 *N* sodium hydroxide: a red color is produced. Then add 0.25 ml. of 0.02 *N* hydrochloric acid: the original yellow color returns.

Sodium Cyanide, NaCN—49.01—White fragments or granules, freely soluble in water; slightly soluble in alcohol.

Caution: Because of the extremely poisonous nature of this reagent itself and of the gas evolved from it on treatment with acids, all tests must be made in a hood with a strong draft, and special care must be taken to avoid inhalation of the fumes. Pipets must not be used in measuring its solutions.

Assay—Weigh accurately about 400 mg. and dissolve it in 30 ml. of water. Add 4 drops of potassium iodide solution (1 in 10) and 1 ml. of stronger ammonia water, and titrate with 0.1 *N* silver nitrate to a slight permanent yellowish turbidity. Each ml. of 0.1 *N* silver nitrate is equivalent to 9.802 mg. of NaCN. Not less than 95% of NaCN is found.

Phosphate—Dissolve 1 g. in 5 ml. of water, add 2 ml. of hydrochloric acid, and evaporate to dryness in a well-ventilated hood. Add 5 ml. of dilute hydrochloric acid (1 in 2) and again evaporate to dryness. Dissolve the residue in 50 ml. of 0.5 *N* sulfuric acid: a 5-ml. portion of this solution shows no more phosphate than corresponds to 0.02 mg. of PO_4 (0.02%).

Lead, page 813—Dissolve 500 mg. in 10 ml. of water in a separator. Add 5 ml. of ammonium citrate solution, 2 ml. of hydroxylamine hydrochloride solution, and 2 drops of phenol red T.S., and make the solution alkaline, if necessary, by the addition of stronger ammonia water. Add 5 ml. of dithizone standard solution, shake gently but well for 1 minute, and allow the layers to separate: any color produced in the chloroform layer is not darker than that produced in a control containing 0.002 mg. of added Pb and 100 mg. of sample (5 parts per million).

Solution A—For the tests which follow, prepare *Solution A* by dissolving 10 g. in water, filtering if necessary, and diluting to 200 ml.

Chloride—Dilute 1 ml. of *Solution A* to 50 ml. To 10 ml. of this solution add 5 ml. of 30% hydrogen peroxide, and cover the beaker until the reaction ceases. Digest on a steam bath for 30 minutes, cool, and neutralize with nitric acid. Dilute to 25 ml., and add 1 ml. of nitric acid and 1 ml. of silver nitrate T.S.: any turbidity produced does not exceed that produced in a control containing 0.015 mg. of added Cl(0.15%).

Sulfate—To 16 ml. of *Solution A* add 10 ml. of hydrochloric acid and evaporate to dryness *under a hood.* Warm the residue with 50 ml. of water and 1 ml. of hydrochloric acid, filter if necessary, and dilute to 100 ml. Heat to boiling, add 5 ml. of barium chloride T.S., digest on a steam bath for 2 hours, and allow to stand overnight. If a precipitate is formed, filter, wash, ignite, and weigh: the residue weighs not more than 1.0 mg. more than the residue obtained in a complete blank test (0.05%).

Sulfide—To 10 ml. of *Solution A* add 10 ml. of water and 3 drops of alkaline lead solution (made by adding sodium hydroxide T.S. to a solution of lead acetate (1 in 10) until the precipitate is redissolved): any color produced is not darker than that produced in a control containing 0.025 mg. of S (50 parts per million).

Thiocyanate—To 20 ml. of *Solution A* add 4 ml. of hydrochloric acid and 4 drops of ferric chloride T.S.: any red color produced within 5 minutes is not darker than that produced in a control prepared by adding 4 ml. of hydrochloric acid and 4 drops of ferric chloride T.S. to 20 ml. of water (about 0.020%).

Iron, total—To 4 ml. of *Solution A*, contained in a platinum dish, add 3 ml. of hydrochloric acid, and evaporate to dryness *in a hood.* Heat for 30 minutes at about 650°. Cool, add 2 ml. of hydrochloric acid and 10 ml. of water, cover the dish with a watch glass, digest on a steam bath until solution is complete, and dilute to 50 ml.: the iron in this solution corresponds to not more than 0.01 mg. of Fe (50 parts per million).

Sodium Molybdate, $Na_2MoO_4.2H_2O$—241.95—A fine, white, odorless, crystalline salt. Soluble in water.

Assay—Dissolve about 1 g., accurately weighed, in 10 ml. of water and 1 ml. of stronger ammonia water. Transfer to a 250-ml. volumetric flask, dilute to volume and mix. To a 50-ml. aliquot, filtered if necessary, in a 600-ml. beaker, add 250 ml. of water, 20 g. of ammonium chloride, 15 ml. of hydrochloric acid and 3 drops of methyl orange T.S. Heat nearly to boiling, and add 18 ml. of lead acetate solution (1 in 10). To the hot and constantly stirred solution add slowly a saturated solution of ammonium acetate until the solution is alkaline, and then add 15 ml. in excess. Digest on a hot plate below boiling temperature until the precipitate has settled. Filter through a porcelain filter crucible, wash 7 or 8 times with a solution containing 10 ml. of nitric acid and 100 ml. of saturated ammonium acetate in 1000 ml., and finally wash 3 times with hot water. Ignite to constant weight in a muffle furnace at 560° to 625°, cool, and weigh: the weight of lead molybdate multiplied by 0.3921, represents the MoO_3; not less than 57% and not more than 59.5% is found.

Insoluble matter—The insoluble matter from 10 g. weighs not more than 0.5 mg. (50 parts per million).

Ammonium—Dissolve 1 g. in 10 ml. of sodium hydroxide solution (1 in 10), dilute to 50 ml., and add 2 ml. of alkaline mercuric-potassium iodide T.S.: any color produced does not exceed that produced in a control containing 0.01 mg. of added NH_4 (10 parts per million).

Chloride—Dissolve 1 g. in 50 ml. of water. To 10 ml. of this solution add 2 ml. of nitric acid, dilute to 25 ml., and add 1 ml. of silver nitrate T.S.: any turbidity does not exceed that in a control containing 0.01 mg. of added Cl (50 parts per million).

Heavy metals—Dissolve 2.5 g. in 15 ml. of sodium hydroxide solution (1 in 10), add 2 ml. of stronger ammonia water, and dilute to 50 ml. To 20 ml. of this dilution add 5 ml. of hydrogen sulfide T.S.: any brown color produced is not darker than that in a control containing 6 ml. of sodium hydroxide solution (1 in 10) and 0.02 mg. of added Pb (20 parts per million).

Iron—To 1.5 g. dissolved in 5 ml. of water, add, in order, 1 ml. of thioglycolic acid solution (5 in 100) and 5 ml. of stronger ammonia water: any color produced is not darker than that in a control containing 500 mg. of sample and 0.01 mg. of added Fe (10 parts per million).

Phosphate—Dissolve 10 g. in 100 ml. of water, add 3.6 ml. of ferric nitrate solution (1 in 10) and 5 ml. of stronger ammonia water, and warm to coagulate the precipitate. Filter, and wash several times with warm diluted ammonium hydroxide solution (5 in 100). Discard the filtrate and washings, and dissolve the precipitate by pouring a mixture of 15 ml. of nitric acid and 50 ml. of water through the filter, collecting the solution in a 250-ml. glass-stoppered flask. Add, dropwise with constant stirring, 13 ml. of stronger ammonia water, heat to 40°, add 50 ml. of ammonium molybdate T.S., stopper the flask, and shake vigorously for 5 minutes. Allow to stand 2 hours and compare the precipitate with that produced in a control containing 0.05 mg. of added PO_4 and which has been treated in the same manner as the sample: the volume of precipitate in the sample does not exceed that in the control (5 parts per million).

Sulfate—Dissolve 1 g. in hot water, add 5 ml. of nitric acid, and evaporate to dryness on the steam bath. Take up the residue in 5 ml. of diluted hydrochloric acid (1 in 20), filter, and wash to 50 ml. To 10 ml. of this solution add 1 ml. of barium chloride T.S.: any turbidity produced does not exceed that produced in a control containing 0.03 mg. of added SO_4 (0.05%).

Sodium Perchlorate, $NaClO_4 . H_2O$—140.46—Colorless, deliquescent crystals. Decomposes at about 150°. Soluble in 95% alcohol.

Assay—Dry about 1.5 g. at 80° in a vacuum desiccator to constant weight. Mix 750 mg., accurately weighed, of the dried and powdered sample with 5 g. of powdered sodium nitrite in a nickel crucible, cover the crucible, and heat it over a free flame until the mixture is well melted. Maintain it in this state, without raising the temperature much higher, for 30 minutes. Allow to cool, add 20 ml. of hot water and digest until the melt is dissolved. Filter into a 200-ml. volumetric flask and wash any undissolved matter thoroughly with hot water, cool, dilute with water to volume, and mix.

Transfer 50.0 ml. of the solution into a 250-ml., glass-stoppered flask, add 25.0 ml. of 0.1 *N* silver nitrate, then add slowly 6 ml. of dilute nitric acid (1 in 6), and heat on the steam bath to expel oxides of nitrogen. Cool, add 3 ml. of nitrobenzene, shake well for 1 to 2 minutes, then add 4 ml. of ferric ammonium sulfate T.S., and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate. Perform a complete blank determination and make any necessary correction. Each ml. of 0.1 *N* silver nitrate is equivalent to 12.24 mg. of $NaClO_4$. Not less than 98.0% $NaClO_4$ is found.

Insoluble matter—Dissolve 10 g. in 50 ml. of water, heat to boiling and filter through a tared sintered-glass crucible. Wash well with water, rinsing the beaker thoroughly. Dry at 105° for two hours and weigh. The weight of the insoluble residue does not exceed 1 mg. (0.01%).

Chlorate and chloride (as Cl)—Dissolve 1 g. in 10 ml. of water, add 1 ml. of 0.1 *N* ferrous sulfate, and heat on the steam bath for 15 minutes. Cool, dilute with water to 50 ml., and add 1 ml. of nitric acid and 1 ml. of silver nitrate T.S. Any turbidity does not exceed that produced by 0.1 mg. of chloride (Cl) contained in a similarly treated blank (0.01% Cl).

Sulfate—Dissolve 1 g. in 10 ml. of water and add 0.05 ml. of diluted hydrochloric acid and 1 ml. of barium chloride T.S. Any turbidity produced in 10 minutes does not exceed that produced in a blank containing 0.05 mg. of added SO_4 (50 parts per million).

Calcium—Dissolve 500 mg. in 10 ml. of hot water, add 0.25 ml. of ammonia T.S. and 3 ml. of ammonium oxalate T.S. and keep the solution hot. No turbidity is produced in 5 minutes (about 0.02%).

Heavy metals—Dissolve 1 g. in 25 ml. of water: the heavy metals limit is 20 parts per million.

***p*-Sodium Periodate,** $Na_3H_2IO_6$—293.89—A white, odorless powder with a slightly saline taste. Very slightly soluble in purified water; freely soluble in the presence of hydrochloric acid. Practically insoluble in alcohol, in ether, or in chloroform.

Assay—To a 500-ml. conical flask add 120 mg. accurately weighed, and add 200 ml. of water, 5 ml. of hydrochloric acid, and 2.5 g. of potassium iodide. Swirl the flask gently for 15 seconds and titrate immediately with 0.1 *N* sodium thiosulfate. When the solution becomes faintly yellow, add 1 ml. of starch T.S. and continue the titration until the solution is colorless. Each ml. of 0.1 *N* sodium thiosulfate is equivalent to 3.674 mg. of $Na_3H_2IO_6$. It shows not less than 98.5% of $Na_3H_2IO_6$.

Loss on drying—It loses not more than 1% of its weight when dried to constant weight at 105°.

Reaction—A solution is alkaline to litmus.

Chloride and bromide—Mix 1 g. with 2 g. of sucrose and ignite carefully at a low temperature, taking small portions at a time. Treat the residue with 10 ml. of hot water, and 1 ml. of nitric acid (1 in 5), filter and wash with 10 ml. of hot water. Cool and add 6 ml. of stronger ammonia water. Add 20 ml. of silver nitrate solution (1 in 20) with constant stirring, dilute to 50 ml. and filter. To 25 ml. of the filtrate add a slight excess of nitric acid. The turbidity is not greater than that produced by 0.25 mg. of chloride ion in an equal volume of solution containing the same quantities of the same reagents (about 0.05% Cl).

Iodide—Dissolve 1 g. in a mixture of 10 ml. of water and 10 ml. of diluted sulfuric acid and add 1 ml. of chloroform: no red-purple color is produced in the chloroform in 1 minute (about 0.01% I).

Manganese—Add 1 g. to 200 ml. of water and 10 ml. of nitric acid. Add 2 ml. of phosphoric acid and heat to boiling for 1 minute: no pink color is developed.

Sulfate—Evaporate 2 g. to dryness with 10 ml. of hydrochloric acid and repeat the evaporation twice with 5-ml. portions of the acid: the residue dissolved in 25 ml. of water shows no more sulfate than corresponds to 0.1 mg. of SO_4 (50 parts per million).

Heavy metals—To 2 g. add 5 ml. of water and 10 ml. of hydrochloric acid and evaporate to dryness on a steam bath.

Repeat the evaporation twice with 5 ml. of hydrochloric acid. Dissolve the residue in 20 ml. of water and add 2 ml. of diluted acetic acid. If this is yellowish, discharge the color with 1 or 2 drops of sodium thiosulfate T.S. and add the same quantity to the control. Dilute to 30 ml. with water, transfer to a color-comparison tube and proceed with the test for heavy metals in reagents. The heavy metals limit is 20 parts per million.

Iron—The iron in 2 g. corresponds to not more than 0.04 mg. of Fe (20 parts per million).

Sodium Phosphate, Tribasic, $Na_3PO_4 \cdot 12H_2O$—380.12—Colorless or white crystals. Freely soluble in water; insoluble in alcohol. [NOTE: This salt when stored under ordinary conditions may lose some water of crystallization. Any loss in water will result in an assay of more than 100% $Na_3PO_4 \cdot 12H_2O$ but does not affect the determination of the relative amount of free alkali present.]

Assay—Accurately weigh 13 to 14 g. and dissolve in 40 ml. of water in a 400-ml. beaker. Add 100.0 ml. of 1 N hydrochloric acid and pass a stream of carbon dioxide-free air, in fine bubbles, through the solution for 30 minutes to expel carbon dioxide. The beaker must be covered with a perforated cover to prevent loss of any of the solution by spraying. Wash down the cover and sides of beaker. Titrate the solution with 1 N sodium hydroxide to a pH of 4.00 as measured with a standardized pH meter and glass electrode system. Calculate (A) the milliliters of 1 N hydrochloric acid consumed in this titration. Protect the solution from absorbing carbon dioxide from the air and continue the titration to pH 8.80 with 1 N sodium hydroxide. Calculate (B) the milliliters of 1 N sodium hydroxide consumed in this titration. If A is equal to or greater than $2B$, then,

$$\frac{B \times 0.3801}{\text{Wt. of sample}} \times 100 = \%\ Na_3PO_4 . 12H_2O$$

If A is less than $2B$, then,

$$\frac{(A - B) \times 0.3801}{\text{Wt. of sample}} \times 100 = \%\ Na_3PO_4 . 12H_2O$$

Excess alkali—Calculate the amount of excess alkali as NaOH from the titration values obtained in the test for *Assay*. If A is equal to or less than $2B$, there is no excess alkali present when the salt is dissolved. If A is greater than $2B$, then

$$\frac{(A - 2B) \times 0.040}{\text{Wt. of sample}} \times 100 = \%\ NaOH$$

Not more than 2.5% is found.

Insoluble matter—Dissolve 10 g. in 100 ml. of water, add 0.10 ml. of methyl red T.S., and add hydrochloric acid until the solution is slightly acid to the methyl red indicator. Heat the solution to boiling and digest in a covered beaker on the steam bath for 1 hour. Filter through a tared filtering crucible, wash thoroughly, and dry at 105°. The weight of the residue should not exceed 1 mg. (0.010%).

Chloride—Dissolve 1 g. in 20 ml. of water, filter if necessary through a chloride-free filter, and add 3 ml. of nitric acid and 1 ml. of silver nitrate T.S. Any turbidity should not exceed that produced by 0.01 mg. of chloride ion (Cl) in an equal volume of solution containing the quantities of reagents used in the test (10 parts per million).

Nitrogen compounds—Dissolve 1 g. in 60 ml. of water in a flask connected through a spray trap to a condenser, the end of which dips beneath the surface of 10 ml. of 0.1 N hydrochloric acid. Add to the flask 10 ml. of freshly boiled sodium hydroxide solution (1 in 10) and 0.5 g. of aluminum wire in small pieces, allow to stand for 1 hour, and distil about 35 ml. To the distillate add 1 ml. of the sodium hydroxide solution, dilute with water to 50 ml. and add 2 ml. of alkaline mercuric potassium iodide T.S. Any color should not exceed that produced when a quantity of an ammonium salt containing 0.01 mg. of nitrogen (N) is treated exactly like the sample (10 parts per million).

Sulfate—Dissolve 5 g. in 100 ml. of water, filter if necessary, add 4 ml. of hydrochloric acid and heat to boiling. Add 5 ml. of barium chloride T.S., digest in a covered beaker on the steam bath for 2 hours, and allow to stand overnight. If a precipitate is formed, filter, wash thoroughly, and ignite. The weight of the precipitate should not be more than 12 mg. greater than the weight obtained from a complete blank test (0.010%).

Arsenic—A solution of 1 g. in 35 ml. of water meets the requirements of the *Arsenic Test*, page 777 (5 parts per million).

Heavy metals—Dissolve 4 g. in about 20 ml. of water, add 8 ml. of 2 N hydrochloric acid, and dilute with water to 32 ml. For the control add 0.02 mg. of lead ion (Pb) to an 8-ml. aliquot of the solution and dilute with water to 25 ml. For the sample dilute the remaining 24-ml. portion with water to 25 ml. Adjust the pH of the control and sample solutions to between 3.0 and 4.0 (using short-range pH indicator paper) with 1 N acetic acid or ammonium hydroxide T.S., dilute with water to 40 ml., and mix. Add 10 ml. of freshly prepared hydrogen sulfide T.S. to each and mix. Any color in the solution of the sample should not exceed that in the control (10 parts per million).

Iron—Dissolve 1 g. in 10 ml. of water and add 3 ml. of 1 N hydrochloric acid. Add 6 ml. of hydroxylamine hydrochloride solution (1 in 10) and 4 ml. of 1,10-phenanthroline solution (made by dissolving 100 mg. of 1,10-phenanthroline monohydrate in 100 ml. of water containing 0.1 ml. of diluted hydrochloric acid) and dilute with water to 25 ml. Any red color should not exceed that produced by 0.01 mg. of iron (Fe) in an equal volume of solution containing the quantities of reagents used in the test, except the 3 ml. of 1 *N* hydrochloric acid. Compare 1 hour after adding the reagents to the sample and standard solutions.

Sodium *p*-Sulfophenylazochromotropate* [*trisodium salt of 4,5-dihydroxy-3-(p-sulfophenylazo)-2,7-naphthalenedisulfonic acid*], $C_{16}H_9N_2Na_3O_{11}S_3 . 3H_2O$—624.46—Bright red powder. Very soluble in water; insoluble in alcohol. Combines with zirconium oxychloride to form a soluble pink zirconium lake.

Strontium Acetate, $Sr(CH_3COO)_2 . {}^1/_2H_2O$—214.72—A white, crystalline powder. Soluble in 3 parts of water; slightly soluble in alcohol.

Assay—Ignite about 3 g., accurately weighed, in a platinum crucible, protecting from sulfur in the flame. Cool, transfer the crucible with the residue to a beaker, and add 50 ml. of water and 40.0 ml. of 1 *N* hydrochloric acid. Boil gently for 30 minutes or longer if necessary, filter, wash with hot water until the washings are neutral, add methyl red T.S., and titrate the excess acid with 1 *N* sodium hydroxide. Each ml. of 1 *N* hydrochloric acid is equivalent to 107.4 mg. of $Sr(CH_3CO_2)_2 . {}^1/_2H_2O$; not less than 99% is found.

Insoluble matter—The insoluble matter from 10 g. weighs not more than 2 mg. (0.02%).

Free alkali, or free acid—Dissolve 3 g. in 30 ml. of water and add 3 drops of phenolphthalein T.S.: no pink color is produced. Now titrate with 0.1 *N* sodium hydroxide to a pink color: not more than 0.3 ml. of the 0.1 *N* sodium hydroxide is required.

Barium—Dissolve 1 g. in 10 ml. of water, and add 1 drop of glacial acetic acid and 5 drops of potassium dichromate solution (1 in 10): no turbidity is produced within 2 minutes (about 0.02%).

Calcium—Ignite 1 g. until completely carbonized. Warm the residue with a mixture of 3 ml. of nitric acid and 10 ml. of water, filter, wash with 5 ml. of water, and evaporate the filtrate to dryness on a steam bath. Powder the residue and dry it at 120° for 3 hours. Reflux the dried powder with 15 ml. of absolute alcohol for 10 minutes, cool in ice, and filter. Repeat the extraction with 10 ml. of absolute alcohol. Evaporate the combined filtrates to dryness, add 0.5 ml. of sulfuric acid, and ignite: the weight of the residue is not more than 10 mg. (0.3% Ca).

Chloride—Dissolve 1 g. in 50 ml. of water, and filter if necessary through a chloride-free filter. To 25 ml. of the solution add 1 ml. of nitric acid and 1 ml. of silver nitrate T.S. Any turbidity does not exceed that produced by 100 mcg. of chloride ion (Cl) in an equal volume of solution containing the quantities of reagents used in the test (0.01%).

Heavy metals—Dissolve 4 g. in about 20 ml. of water, and dilute to 30 ml. For the control, add 20 mcg. of lead ion (Pb) to a 5-ml. portion of the solution, and dilute to 25 ml. with water. For the sample, use the remaining 25-ml. portion. Adjust the pH of each solution to between 3.0 and 4.0 with diluted acetic acid or ammonia T.S., dilute to 40 ml. with water, and mix. Add 10 ml. of hydrogen sulfide T.S. to each solution, and mix. Any color in the sample solution does not exceed that in the control (10 parts per million).

Iron—The iron in 1 g. is not more than 0.01 mg. of Fe (10 parts per million).

Alkali salts—Dissolve 2 g. in 80 ml. of water, heat to boiling, add an excess of ammonium carbonate T.S., boil for 5 minutes, dilute to 100 ml., and filter. Evaporate 50 ml. of the filtrate and ignite: the residue after correcting for the ignition residue from half the volume of the clear ammonium carbonate T.S. used above, is not more than 3 mg. (0.3%).

Nitrate—Dissolve 1 g. in 10 ml. of water, add 0.1 ml. of indigo carmine T.S. and then add 10 ml. of sulfuric acid: the blue color persists for 5 minutes (about 0.01% NO_3).

Styrene-divinylbenzene Anion Exchange Resin, 50–100 mesh—A strongly basic, crosslinked resin containing quaternary ammonium groups and about 4% divinylbenzene. It consists of tan colored beads which may be relatively free flowing. It is available in the chloride form which can be converted to the hydroxide form by regeneration with a sodium hydroxide solution (5 in 100). For satisfactory regeneration a contact time of at least 30 minutes is required after which it must be washed free of excess alkali. It is insoluble in water, in methanol and in acetonitrile.

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* The reagent is available as Catalog No. 7309 from Distillation Products Industries, Eastman Organic Chemicals Dept., Rochester NY 11203. A procedure for its preparation is described in *Z. Anal. Chem.*, **146**, 417 (1955).

Suitable for use in column chromatography.*

Moisture content of fully regenerated and expanded resin—Transfer 10 to 12 ml. of the resin (as received) to a flask and convert it completely to the chloride form by stirring with 150 ml. of hydrochloric acid (5 in 100) for a minimum time of 30 minutes. Decant the acid and wash the resin in the same manner with distilled water until the wash water is neutral to litmus paper.

Transfer 5 to 7 ml. of the regenerated resin to a glass filtering crucible and remove only the excess surface water by very careful suction filtration. Transfer the conditioned, dried resin to a tared weighing bottle and weigh. Dry in a vacuum oven at 100° to 105° and 50 mm. of mercury for 16 hours. Transfer from the vacuum oven to a desiccator and cool to room temperature. Reweigh. The loss in weight is between 50 and 65%.

Total net volume capacity—Transfer 2.5 to 3 ml. of the conditioned, undried (see *Moisture content* above) resin to a 5-ml. graduated cylinder and fill it with water. Remove any air bubbles from the resin bed with a stainless steel wire and settle the resin to its minimum volume by tapping the graduated cylinder. Record the volume of the resin.

Transfer the resin to a 250-ml. flask with 100 ml. of water. Add 2 ml. of sulfuric acid and heat to 70° to 80° and hold at that temperature for 5 minutes with occasional stirring (do not boil). Cool to room temperature, and add 2.5 ml. of nitric acid (1 in 2), 2 ml. of ferric ammonium sulfate T.S., and 0.20 ml. of 0.1 N ammonium thiocyanate. Titrate with 0.1 N silver nitrate until the solution turns colorless and add a measured excess (1 to 5 ml.). Heat to boiling to coagulate the silver chloride precipitate. Cool to room temperature and add 10 ml. of nitrobenzene, shake vigorously and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate.

$$\frac{\text{net ml. } AgNO_3 \times N}{\text{ml. of resin}} = \text{meq./ml.}$$

The total exchange capacity of the regenerated, wet resin is more than 1.0 meq. per ml.

Wet screen analysis—The purpose of this test is to identify properly the mesh size of the resin. To obtain an accurate screen analysis would require special apparatus and technique.

Add 150 ml. of resin to 200 ml. of distilled water in an appropriate bottle and allow it to stand at least 4 hours to completely swell the resin.

Transfer by means of a graduated cylinder 100 ml. of settled and completely swollen resin to the top screen of a series (20, 50, 100 mesh) of 20.3-cm. brass screens. Thoroughly wash the resin on each screen with a stream of distilled water until the resin is completely classified, collecting the wash water in a suitable container. Wash the beads remaining on the respective screens back into the 100-ml. graduate and record the volume of settled resin on each screen. Not less than 80% of the resin is between 50 and 100 mesh.

Sulfosalicylic Acid, $C_6H_3(COOH)(OH)(SO_3H)$-1,2,5.$2H_2O$—254.22—White or not more than slightly pinkish, needle-like crystals or a crystalline powder. Soluble in water and in alcohol.

Assay—Weigh accurately about 5 g., dissolve in 50 ml. of water, add phenolphthalein T.S., and titrate with 1 N sodium hydroxide. Each ml. of 1 N sodium hydroxide is equivalent to 127.1 mg. of $C_6H_3OH.SO_3H.COOH.2H_2O$. Between 99.0 and 101.0% is found.

Residue on ignition—Gently ignite 1 g., cool, add 1 ml. of sulfuric acid, and reignite gently until the carbon and excess acid are removed, then ignite at 800 ± 25° for 15 minutes: the residue weighs not more than 1.0 mg. (0.10%).

Sulfate—Dissolve 1 g. in 20 ml. of water, neutralize with ammonia T.S., using phenolphthalein T.S. as indicator, and dilute to 40 ml. To 10 ml. add 1 ml. of dilute hydrochloric acid (1 in 20) and 1 ml. of barium chloride T.S.: any turbidity produced in 10 minutes does not exceed that in a control containing 0.05 mg. of added SO_4 (about 0.02%).

Salicylic acid—Dissolve 5 g. in 25 ml. of water, add 0.5 ml. of hydrochloric acid, and transfer to a separator. Add 25 ml. of chloroform, shake for 5 minutes, allow to separate, and draw off the chloroform into a second separator. Wash the chloroform twice with 5-ml. portions of water, then filter through a small filter paper moistened with chloroform and evaporate the filtrate at room temperature to dryness. Dissolve the residue in 50 ml. of warm water, cool to room temperature, and add 0.5 ml. of freshly prepared ferric ammonium sulfate T.S.: any color produced is not darker that that produced in a control containing 1.0 mg. of added salicylic acid (0.02%).

Insoluble matter—Five g., dissolved in 50 ml. of water, shows not more than 1.0 mg. of insoluble matter (0.02%).

Tetra-*n*-Butylammonium Iodide, $(C_4H_9)_4NI$—369.38—White, shiny, crystalline flakes. Soluble in alcohol and in ether; slightly soluble in water.

Assay—Dissolve 1.000 g. in 100 ml. of boiling water, with vigorous stirring, and cool to room temperature. Stir the solution mechanically, add 5.0 ml. of diluted nitric acid, and titrate potentiometrically with 0.1 *N* silver nitrate using a glass-silver electrode system with a suitable pH meter; add the titrant in 0.10-ml. increments near the end-point. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* silver nitrate is equivalent to 36.94 mg. of $(C_4H_9)_4NI$. Not less than 99.9% is found.

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* A suitable resin is that known as "Dowex 1X4," produced by The Dow Chemical Company, Midland, MI 48640, and available through J. T. Baker Chemical Company, Phillipsburg, NJ 08865.

Melting range, page 814—Between 146° and 147°.

Tetraethylammonium Hydroxide, $(C_2H_5)_4NOH$—147.26—This base is known only in solution or as solid tetra- or hexahydrate. In commerce it is usually available as a 10% or 25% aqueous solution. This solution is clear, colorless and has a strong ammonia-like odor. Tetraethylammonium hydroxide is a strong base, absorbing CO_2 from the air. Sp. gr. of the 10% solution is about 1.01. Keep in tightly closed containers.

Assay—Accurately weigh a glass-stoppered flask with about 15 ml. of water. Add a quantity of the solution equivalent to about 500 mg. of $(C_2H_5)_4NOH$ and reweigh. Titrate the solution with 0.1 *N* hydrochloric acid, using methyl red T.S. as indicator. Each ml. of 0.1 *N* hydrochloric acid is equivalent to 14.73 mg. of $(C_2H_5)_4NOH$. Not less than 98.0% of the labeled amount is found.

Other amines—Weigh accurately a quantity of the solution corresponding to about 500 mg. of $(C_2H_5)_4NOH$ in a wide weighing bottle tared with 5 ml. of water. Add a slight excess of 1 *N* hydrochloric acid (about 5 ml.), evaporate to dryness on the steam bath, and dry at 105° for 2 hours. The weight of the tetraethylammonium chloride so obtained multiplied by 0.8883 represents the quantity of $(C_2H_5)_4NOH$ in the weight of the sample taken for the test, and it corresponds to within 1% of that found in the *Assay*, the percentage found in the *Assay* representing 100%.

Residue on evaporation—Evaporate 5 ml. on the steam bath and dry at 105° for 1 hour. The weight of the residue does not exceed 1.0 mg. (0.02%). (Save the residue.)

Heavy metals—To the residue obtained in the test for *Residue on evaporation* add 0.25 ml. of nitric acid and 1 ml. of water, and evaporate to dryness on the steam bath. Take up the residue in 1 ml. of 1 *N* acetic acid and 5 ml. of hot water, and dilute with water to 25 ml.: the heavy metals limit is 5 parts per million.

Thimerosal—Use *Thimerosal,* page 703.

o-**Tolidine** (*4,4′-diamino-3,3′-dimethylbiphenyl*), $(NH_2)(CH_3)C_6H_3.C_6H_3(CH_3)(NH_2)$-4,3,3′,4′—212.30—White to reddish crystals or crystalline powder. Slightly soluble in water; soluble in alcohol, in ether, and in dilute acids.

Melting range, page 814—Between 129° and 131°.

Storage—Preserve in well-closed containers protected from light.

p-**Toluenesulfonyl-L-arginine Methyl Ester Hydrochloride,** $C_{14}H_{22}N_4O_4S.HCl$—378.88—Determine suitability for use as a substrate as directed under *Chymotrypsin,* page 168.

o-**Toluidine** (*2-aminotoluene, 2-methylaniline*), $C_6H_4(CH_3)(NH_2)$-1,2—107.16—A light yellow liquid becoming reddish brown on exposure to air and light. Slightly soluble in water; soluble in alcohol, in ether, and in dilute acids. Preserve in well-closed containers protected from light.

Specific gravity, page 866—The specific gravity is 1.008 at 20°.

Boiling range—Between 200° and 202°.

Tyrosine, $C_9H_{11}NO_3$—181.19—Colorless or white crystals, or white, crystalline powder. Slightly soluble in water; insoluble in most organic solvents. Soluble in diluted hydrochloric acid and in solutions of alkali hydroxides and carbonates.

Solubility—Separate 200-mg. portions dissolve completely in 10 ml. of 1 *N* hydrochloric acid and in 10 ml. of sodium carbonate T.S., yielding solutions that are clear and colorless.

Specific rotation, page 822—Its specific rotation, determined in a 4 percent solution in 1 *N* hydrochloric acid, is between -9.8 and $-11.2°$.

Nitrogen—Determine the nitrogen in a sample, previously dried at 105° for 2 hours: between 7.5 and 7.9% of N is found.

Residue on ignition—It yields not more than 0.1% of residue on ignition.

Ammonium salts—To 200 mg. add 5 ml. of sodium carbonate T.S., and bring the solution to a boil: the odor of ammonia is not evolved.

Xylene, $C_6H_4(CH_3)_2$—106.17—A colorless, transparent, flammable liquid. Insoluble in water; very soluble in alcohol and in ether. Specific gravity: 0.85.

Boiling range, Method II, page 782—Distil 100 ml.: not less than 95 ml. distils between 137° and 140°.

Residue on evaporation—Evaporate 115 ml. on a steam bath, and dry at 110° for 1 hour: the residue weighs not more than 2 mg. (0.002%).

Sulfur compounds—Place 30 ml. of alcoholic potassium hydroxide T.S. in a conical flask, add 6 ml. of sample, and boil the mixture gently for 30 minutes under a reflux condenser. Detach the condenser, dilute with 50 ml. of water, and heat on a steam bath until the benzene and alcohol are evaporated. Add 50 ml. of bromine T.S., and heat for 15 minutes longer. Transfer the solution to a beaker, neutralize with dilute hydrochloric acid (1 in 4), add an excess of 1 ml. of the acid, and concentrate to about 50 ml. Filter if necessary, heat the filtrate to boiling, add 5 ml. of barium chloride T.S., heat on a steam bath for 2 hours, and allow to stand overnight. If a precipitate is formed, filter through a small filter paper, wash with water until the last washing does not react with silver nitrate T.S., and ignite: the residue weighs not more than 1.2 mg., correction being made for a blank (0.003% as S).

Substances darkened by sulfuric acid—Shake 15 ml. with 5 ml. of sulfuric acid for 15 to 20 seconds, and allow to stand for 15 minutes: the xylene layer is colorless, and the color of the acid does not exceed that of a mixture of 1 volume of water and 3 volumes of a color standard containing 5 g. of $CoCl_2.6H_2O$, 40 g. of $FeCl_3.6H_2O$, and 20 ml. of hydrochloric acid in 1000 ml.

Water—Determine by the titrimetric method: not more than 0.03% is found.

Zinc Acetate, $Zn(CH_3COO)_2.2H_2O$—219.49—Colorless crystals or white, crystalline plates, having a slight odor of acetic acid. One g. dissolves in about 2.5 ml. of water and in about 30 ml. of alcohol.

Insoluble matter—Twenty g., dissolved in 200 ml. of water and 2 ml. of glacial acetic acid, shows not more than 1.0 mg. of insoluble matter (0.05%).

Chloride—Two g. shows not more than 0.01 mg. of Cl (5 parts per million).

Nitrate—Dissolve 1 g. in 10 ml. of water, and 0.05 ml. of indigo carmine T.S., and then add 10 ml. of sulfuric acid: the blue color persists for 5 minutes (about 50 parts per million).

Sulfate—Dissolve 20 g. in 200 ml. of water, add 1 ml. of hydrochloric acid, and filter. Heat the filtrate to boiling, add 10 ml. of barium chloride T.S., heat on a steam bath for 2 hours, and allow to stand overnight. If a precipitate is formed, filter through a small filter paper, wash with water, and ignite: the residue weighs not more than 1.0 mg. (20 parts per million as SO_4).

Alkalies and earths—Dissolve 2 g. in 140 ml. of water, add 10 ml. of stronger ammonia water, completely precipitate the zinc with hydrogen sulfide, and filter. To 75 ml. of the filtrate add 5 drops of sulfuric acid, evaporate, and ignite: the residue weighs not more than 1 mg. (0.1%).

Arsenic, page 777—Dissolve 25 g. in water: the limit for As is 0.5 part per million.

Iron—Two g. shows not more than 0.01 mg. of Fe (5 parts per million).

Lead, page 813—Dissolve 1 g. in 20 ml. of water. To 5 ml. of the solution add 0.02 mg. of Pb and 12 ml. of potassium cyanide solution (3 in 20), and dilute to 50 ml. (A). To the remaining 15 ml. add 12 ml. of the potassium cyanide solution, and dilute to 50 ml. (B). Then to each add 5 drops of sodium sulfide T.S.: B is not darker than A (40 parts per million).

Zirconium Oxychloride, $ZrOCl_2.8H_2O$—322.25—White, silky needles. Soluble in water, in ethanol, and in methanol; insoluble in chloroform and in hexane. Its solutions in water are acid to litmus.

TEST SOLUTIONS (T.S.)

Albumen T.S.—Carefully separate the white from the yolk of a strictly fresh hen's egg. Shake the white with 100 ml. of water until thoroughly mixed and all but the chalaza has undergone solution, then filter. Prepare the solution fresh.

Alcohol-Phenol T.S.—Dissolve 780 mg. of phenol in sufficient alcohol to make 100 ml.

Ammonium Polysulfide T.S.—A yellow liquid, made by saturating ammonium sulfide T.S. with sulfur.

Barfoed's Reagent—See *Cupric Acetate T.S., Stronger.*

Blue Tetrazolium T.S.—Dissolve 500 mg. of blue tetrazolium in alcohol to make 100 ml.

Cupric Acetate T.S.—Dissolve 100 mg. of cupric acetate in about 5 ml. of water to which a few drops of acetic acid has been added. Dilute to 100 ml., and filter if necessary.

Cupric Acetate T.S., Stronger (*Barfoed's Reagent*)—Dissolve 13.3 g. of cupric acetate in a mixture of 195 ml. of water and 5 ml. of acetic acid.

Cupric-Ammonium Sulfate T.S.—To cupric sulfate T.S. add ammonia T.S., dropwise, until the precipitate at first formed is nearly but not completely dissolved. Allow to settle, and decant the clear solution. Prepare this solution fresh.

Diiodofluorescein T.S.—Dissolve 500 mg. of diiodofluorescein in a mixture of 75 ml. of alcohol and 30 ml. of water.

Dinitrophenylhydrazine T.S.—Add 2 g. of 2,4-dinitrophenylhydrazine to a cooled mixture of 10 ml. of sulfuric acid and 10 ml. of water and shake in a glass-stoppered flask until dissolved. Add 35 ml. of water, mix, cool, and filter.

Folin-Ciocalteu Phenol T.S.—Into a 1500-ml. flask introduce 100 g. of sodium tungstate, 25 g. of sodium molybdate, 700 ml. of water, 50 ml. of phosphoric acid, and 100 ml. of hydrochloric acid. Reflux the mixture gently for about 10 hours and add 150 g. of lithium sulfate, 50 ml. of water, and a few drops of bromine. Boil the mixture, without the condenser, for about 15 minutes or until the excess bromine is expelled. Cool, dilute to 1 liter, and filter. The reagent should have no greenish tint. Dilute a portion of the reagent with an equal volume of water before use.

8-Hydroxyquinoline T.S.—Dissolve 5 g. of 8-hydroxyquinoline in sufficient alcohol to make 100 ml.

Iodine T.S.—Use 0.1 *N* Iodine.

Iron-phenol T.S. (*Iron-Kober reagent*)—Dissolve 1.054 g. of ferrous ammonium sulfate in 20 ml. of water, and add 1 ml. of sulfuric acid and 1 ml. of 30% hydrogen peroxide. Mix, heat until effervescence ceases, and dilute to 50 ml. To 3 volumes of this solution contained in a volumetric flask add sulfuric acid, with cooling, to make 100 volumes. Purify phenol by distillation, discarding the first 10 percent and the last 5 percent, collecting the distillate, with exclusion of moisture, in a dry, tared glass-stoppered flask of about twice the volume of the phenol. Solidify the phenol in an ice bath, breaking the top crust with a glass rod to ensure complete crystallization. Weigh the flask and its contents, add to the phenol 1.13 times its weight of the iron-sulfuric acid solution prepared as directed, stopper the flask, and allow to stand, without cooling but with occasional mixing, until the phenol is liquefied. Shake the mixture vigorously until mixed, allow to stand in the dark for 16 to 24 hours, and again weigh the flask and its contents. To the mixture add 23.5% of its weight of a solution of 100 volumes of sulfuric acid in 110 volumes of water, mix, transfer to dry glass-stoppered bottles, and store in the dark, protected from atmospheric moisture. Use within 6 months. Dispense the reagent from a small-bore buret, arranged to exclude moisture, capable of delivering 1 ml. in 30 seconds or less, and having no lubricant, other than reagent, on its stopcock. Wipe the buret tip with tissue before each addition.

Lead Acetate T.S., Alcoholic—Dissolve 2 g. of clear, transparent crystals of lead acetate in sufficient alcohol to make 100 ml. Store in tight containers.

Lead Solution, Standard—See page 813.

Litmus T.S.—Digest 25 g. of powdered litmus with three successive, 100-ml. portions of boiling alcohol, continuing each extraction for about 1 hour. Filter, wash with alcohol, and discard the alcohol filtrate. Macerate the residue with about 25 ml. of cold water for 4 hours, filter, and discard the filtrate. Finally digest the residue with 125 ml. of boiling water for 1 hour, cool, and filter.

Methyl Red T.S., Methanolic—Dissolve 1 g. of methyl red in 100 ml. of methanol, and filter if necessary.

Phloroglucinol T.S.—Dissolve 500 mg. of phloroglucinol in 25 ml. of alcohol. Store in tight containers, protected from light.

Potassium Carbonate T.S.—Dissolve 7 g. of anhydrous potassium carbonate in sufficient water to make 100 ml.

Palladium Chloride T.S., Buffered—Weigh 500 mg. of palladous chloride into a 250-ml. beaker, add 5 ml. of concentrated hydrochloric acid and warm the mixture on a steam bath. Add 200 ml. of hot water in small increments with continued heating until solution is complete. Transfer the solution to a 500-ml. volumetric flask and dilute to volume with water. Transfer 50 ml. to a 100-ml. volumetric flask. Add 10 ml. of 1 *M* sodium acetate and 9.6 ml. of 1 *N* HCl. Dilute to volume with water.

Potassium Iodoplatinate T.S.—Dissolve 200 mg. of platinic chloride in 2 ml. of water, mix with 25 ml. of potassium iodide solution (1 in 25), and dilute with water to 50 ml.

Potassium Sulfate T.S.—Dissolve 1 g. of potassium sulfate in sufficient water to make 100 ml.

Pyrogallol T.S., Alkaline—Dissolve 500 mg. of pyrogallol in 2 ml. of water. Dissolve 12 g. of potassium hydroxide in 8 ml. of water. The solutions should be freshly prepared and mixed immediately before use.

Resorcinol T.S.—Dissolve 1 g. of resorcinol in sufficient hydrochloric acid to make 100 ml.

Silver Diethyldithiocarbamate T.S.—Dissolve 1 g. of silver diethyldithiocarbamate in 200 ml. of redistilled pyridine. Store the solution in a light-resistant container, and use within one month.

Sodium Alizarinsulfonate T.S.—Dissolve 100 mg. of sodium alizarinsulfonate in 100 ml. of water, and filter.

Sodium Aminoacetate T.S. (*Sodium Glycinate T.S.*)—Dissolve 3.75 g. of aminoacetic acid in about 500 ml. of water, add 2.1 g. of sodium hydroxide, and dilute to 1000 ml. Mix 9 ml. of the resulting solution with 1 ml. of dilute glacial acetic acid (1 in 300). This test solution has a pH between 10.4 and 10.5.

Sodium Chloride T.S., Alkaline—Dissolve 2 g. of sodium hydroxide in 100 ml. of water, saturate the solution with sodium chloride, and filter.

Sodium Fluoride T.S.—Dry about 500 mg. of sodium fluoride at 200° for 4 hours. Weigh accurately 222 mg. of the dried sodium fluoride, and dissolve it in sufficient water to make 100.0 ml. Dilute 10.0 ml. of the solution with water to 1000.0 ml. Each ml. of this solution corresponds to 0.01 mg. of fluorine (F).

Sodium Hypochlorite T.S.—A clear, pale greenish yellow liquid, having an odor of chlorine. Is affected by light and gradually deteriorates. Store in light-resistant containers, preferably at a temperature not above 25°.

Assay—Weigh accurately in a glass-stoppered flask about 3 ml. of the solution, and dilute it with 50 ml. of water. Add 2 g. of potassium iodide and 10 ml. of acetic acid, and titrate the liberated iodine with 0.1 N sodium thiosulfate, adding starch T.S. as the indicator: each ml. of 0.1 N sodium thiosulfate is equivalent to 3.723 mg. of NaClO. Not less than 4% of NaClO is found.

Sodium Phosphotungstate T.S.—To a solution of 20 g. of sodium tungstate in 100 ml. of water add sufficient phosphoric acid to impart a strongly acid reaction to litmus paper, and filter. When required for use, decant the clear solution from any sediment that may be present. Store in tight, light-resistant containers.

Sodium Tartrate T.S.—Dissolve 11.5 g. of sodium tartrate in sufficient water to make 100 ml.

Sodium Tetraphenylboron T.S.—Dissolve 1.2 g. of sodium tetraphenylboron in water to make 200 ml. If necessary, stir for 5 minutes with 1 g. of freshly prepared hydrous aluminum oxide and filter to clarify.

Sodium Thiosulfate T.S.—Use 0.1 N Sodium Thiosulfate.

Stannous Chloride, Stronger, T.S., Acid—Dissolve 40 g. of stannous chloride, $SnCl_2 . 2H_2O$, in 100 ml. of hydrochloric acid. Store the solution in all-glass containers, and use within 3 months.

Sulfanilic Acid T.S.—Dissolve 800 mg. of sulfanilic acid in 100 ml. of acetic acid. Store in tight containers.

Sulfuric Acid-Formaldehyde T.S.—Add 1 drop of formaldehyde T.S. to each ml. of sulfuric acid, and mix. Prepare this solution fresh.

Tartaric Acid T.S.—Dissolve 3 g. of tartaric acid in sufficient water to make 10 ml. Prepare this solution fresh.

Thorium Nitrate T.S.—Dissolve 1 g. of thorium nitrate in sufficient water to make 100 ml. Filter if necessary.

Triphenyltetrazolium Chloride T.S.—Dissolve 500 mg. of triphenyltetrazolium chloride in dehydrated alcohol to make 100 ml.

VOLUMETRIC SOLUTIONS

All volumetric solutions, whether made by direct solution or by dilution of a stronger solution, must be thoroughly mixed by shaking before standardization. As the strength of a standard solution may change upon standing, the factor should be re-determined frequently.

When solutions of a reagent are used in several normalities, the details of the preparation and standardization are usually given for the normality most frequently required. Stronger or weaker solutions are prepared and standardized in the same general manner as described, using proportionate amounts of the reagent. It is possible in many instances to prepare lower normalities accurately by making an exact dilution of a stronger solution. Volumetric solutions prepared by dilution should be re-standardized either as directed for the stronger solution or by comparison with another volumetric solution having a known ratio to the stronger solution.

Dilute solutions that are not stable, as, for instance, potassium permanganate 0.01 N and more dilute sodium thiosulfate, are preferably prepared by exactly diluting the higher normality with thoroughly boiled and cooled water on the same day they are required for use.

Preparation and Methods of Standardization of Volumetric Solutions—The following directions give only one method for standardization, but other methods of standardization, capable of yielding at least the same degree of accuracy, may be used. For those substances that are available as certified primary standards, or that are available as highly purified substances of primary standard quality, it is permissible to prepare solutions by accurately weighing a suitable quantity of the substance and dissolving it to produce a specific volume of solution of known concentration. Acetic, hydrochloric, and sulfuric acids may be standardized against a sodium hydroxide solution that recently has been standardized against a certified primary standard.

All volumetric solutions, if practicable, are to be prepared, standardized, and used at the standard temperature of 25°. If a titration is carried out at a markedly different temperature, the volumetric solution should be standardized at that same temperature or a suitable temperature correction should be made.

Ceric Sulfate, 0.01 N—Dissolve 5.5 g. of ceric sulfate, $[Ce(HSO_4)_4]$, in about 500 ml. of water containing 28 ml. of sulfuric acid, and dilute to 1 liter. Allow the solution to stand overnight, and filter. Standardize this solution daily as follows: prepare freshly a 0.01 *N* hydroquinone solution by dissolving 275.2 mg. of hydroquinone in sufficient 0.5 *N* alcoholic sulfuric acid to make 500.0 ml. To 25.0 ml. of this solution, add 75 ml. of 0.5 *N* alcoholic sulfuric acid, 20 ml. of water, and 2 drops of diphenylamine T.S. Titrate with the ceric sulfate solution at a rate of approximately 25 drops per 10 seconds until an end-point is reached which persists for 10 seconds. Run a blank test using 100 ml. of 0.5 *N* alcoholic sulfuric acid, 20 ml. of water, and 2 drops of diphenylamine T.S., and make any necessary corrections. Calculate the normality of the ceric sulfate solution by the formula (g. of hydroquinone per liter × 25) ÷ (55.05 × ml. of ceric sulfate solution consumed).

Lithium Methoxide, 0.1 N—Dissolve 600 mg. of freshly cut lithium metal in 150 ml. of methanol, cooling the flask during the addition. When the reaction is complete, add 850 ml. of anhydrous benzene. If cloudiness or precipitation occurs, add a sufficient amount of methanol to clarify the solution. Store the reagent preferably in the reservoir of an automatic buret, protected from carbon dioxide and moisture. Standardize this solution as follows: dissolve about 500 mg. of benzoic acid (National Bureau of Standards primary standard) in 10 ml. of dimethylformamide. Add 5 drops of thymol blue T.S., and titrate to a dark blue end-point with the lithium methoxide solution. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* lithium methoxide is equivalent to 12.21 mg. of benzoic acid.

Potassium Bromide-Potassium Bromate, 0.1 N—Dissolve 2.78 g. of $KBrO_3$ and 12.0 g. of KBr in water and dilute to 1000 ml. Standardize against 0.1 *N* sodium thiosulfate, using starch T.S. as the indicator.

Potassium Iodate, 0.1 N—Dissolve 3.567 g. of potassium iodate, previously dried at 110° to constant weight, in 200 ml. of oxygen-free water containing 1 g. of sodium hydroxide and 10 g. of potassium iodide. Dilute to 1000.0 ml. with oxygen-free water, and mix. The solution can be standardized against a solution prepared from an accurately weighed quantity of reagent tin (Sn) and hydrochloric acid. Each ml. of 0.1 *N* potassium iodate is equivalent to 5.934 mg. of Sn^{++}, to 9.480 mg. of $SnCl_2$, and to 7.835 mg. of SnF_2.

Sulfuric Acid, Alcoholic, 5 N—Add cautiously, with stirring, 139 ml. of sulfuric acid to a sufficient quantity of dehydrated alcohol to make 1000.0 ml.

Sulfuric Acid, Alcoholic, 0.5 N—Add cautiously, with stirring, 13.9 ml. of sulfuric acid to a sufficient quantity of dehydrated alcohol to make 1000.0 ml. It may also be prepared by diluting 100.0 ml. of 5 *N* alcoholic sulfuric acid with sufficient dehydrated alcohol to make 1000.0 ml.

Tetrabutylammonium Hydroxide, 0.1 N—Dissolve 40 g. of tetra-*n*-butylammonium iodide in 90 ml. of anhydrous methanol in a glass-stoppered flask. Place in an ice bath, add 20 g. of powdered silver oxide, stopper the flask, and agitate vigorously for 60 minutes. Centrifuge a few ml., and test the supernatant liquid for iodide (page 808). If the test is positive, add an additional 2 g. of silver oxide and continue to allow to stand for 30 minutes with intermittent agitation. When all of the iodide has reacted, filter through a fine-porosity sintered-glass funnel. Rinse the flask and funnel with three 50-ml. portions of anhydrous benzene, adding the rinsings to the filtrate. Dilute to 1000.0 ml. with anhydrous benzene, and flush the solution for 10 minutes with dry, carbon dioxide-free nitrogen. Store in a reservoir protected from carbon dioxide and moisture, and discard after sixty days. Alternatively, the solution may be prepared by diluting a suitable volume of a commercially available tetrabutylammonium hydroxide solution in methanol with anhydrous benzene. Standardize the solution on the day of use as follows: dissolve about 400 mg. of benzoic acid (National Bureau of Standards primary standard), accurately weighed, in 80 ml. of dimethylformamide, add 3 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate to a blue end-point with the tetrabutylammonium hydroxide solution, delivering the titrant from a buret equipped with a carbon dioxide absorption trap. Perform a blank determination, and make any necessary correction. Each ml. of 0.1 *N* tetrabutylammonium hydroxide is equivalent to 12.21 mg. of benzoic acid.

GENERAL INFORMATION

BALANCES, WEIGHTS, AND MEASURING DEVICES

Prescription Balances

Description—A prescription balance is a scale or balance adapted to weighing medicinal and other substances required in prescriptions or in other pharmaceutical compounding. It is constructed so as to support its full capacity without developing undue stresses, and its adjustment is not altered by repeated weighings of the capacity load. The removable pans should be of equal weight. The balance should have leveling feet or screws. A balance that has a graduated weighbeam must have a stop that halts the rider or poise at the "zero" reading. The reading edge of the rider is parallel to the graduations on the weighbeam. The distance from the face of the index plate to the indicator pointer or pointers should be not more than 1.0 mm. (0.04 inch), the points should be sharp; and when there are two, their ends should not be separated by more than 1.0 mm. (0.04 inch) when the scale is in balance. The indicating elements and the lever system should be protected against drafts, and the balance lid should permit free movement of the loaded weighing pans when the lid is closed. The balance must have a mechanical arresting device.

Definitions—

Capacity—Maximum weight, including the weight of tares, to be placed on one pan. The *N.B.S. Handbook* 44, 3rd ed., states: "*In the absence of information to the contrary,* the nominal capacity of a Class *A* balance shall be assumed to be 15.5 g. ($^1/_2$ apothecaries ounce)." Most of the commercially available Class *A* balances have a capacity of 120 g. (4 ounces) and bear a statement to that effect.

Weighbeam or Beam—A graduated bar equipped with a movable poise or rider. The maximum weight should read 1 g. (about 15 grains) with divisions equal to to 10 mg. (about $^1/_6$ grain).

Tare Bar—An auxiliary ungraduated weighbeam bar with a movable poise. This can be used to correct for variations in weighing-glasses or papers.

Balance Indicator—A combination of elements, one or both of which will oscillate with respect to the other, to indicate the condition of balance.

Rest Point—The point on the index plate at which the indicator or pointer stops when the oscillations of the balance cease; or the index plate position of the indicator or pointer calculated from recorded consecutive oscillations in both directions past the "zero" of the index plate scale. If the balance has a two-pointer indicating mechanism, the position or the oscillations of only one of the pointers need be recorded or used to determine the rest point.

Sensitivity Requirement (*SR*)—The maximum change in load that will cause a specified change in the position of rest of the indicating element or elements of the balance.

Class A Prescription Balance—A balance that meets the tests for this type of balance has a sensitivity requirement of 6 mg. with no load and with a load of 10 g. on each pan. The Class *A* balance should be used for all the weighing operations required in prescription compounding.

Class B Prescription Balance—A balance that meets the tests for a Class *A* balance, but has a maximum maintenance sensitivity requirement of 30 mg. It should be conspicuously marked with the words, "Class *B*—Not to be used in weighing loads of less than 648 mg. (10 grains)," or a statement conveying the same information.

Class *A* and Class *B* prescription balances have the same capacity. The Class *A* balance should be used for all the weighing operations required in prescription compounding.

In order to avoid errors of 5 percent or more which might be due to the limit of accuracy of the Class *A* prescription balance, do not weigh less than 200 mg. (3 grains) of any material. If a smaller weight of dry material is required, mix a larger known weight of the ingredient with a known weight of dry diluent, and weigh an aliquot portion of the mixture for use.

Testing the Prescription Balance—A Class *A* prescription balance meets the following four basic tests. Use a set of test weights and keep the rider on the weighbeam at zero unless directed to change its position. A chart on which to record the test results is available, see page 940.

1. *Sensitivity Requirement*—Level the balance, determine the rest point, and place a 6-mg. weight on one of the empty pans. Repeat the operation with a 10-g. weight in the center of each pan. The rest point is shifted not less than one division on the index plate each time the 6-mg. weight is added.

2. *Arm Ratio Test*—This test is designed to check the equality of length of both arms of the balance. Determine the rest point of the balance with no weight on the pans. Place in the center of each pan a 30-g. test weight and determine the rest

point. If the second rest point is not the same as the first, place a 20-mg. weight on the lighter side; the rest point should move back to the original place on the index plate scale or farther.

3. *Shift Tests*—These tests are designed to check the arm and lever components of the balance.

A. Determine the rest point of the indicator without any weights on the pans.

B. Place one of the 10-g. weights in the center of the left pan, and place the other 10-g. weight successively toward the right, left, front, and back of the right pan, noting the rest point in each case. If in any case the rest point differs from the rest point determined in Step A, add a 10-mg. weight to the lighter side; this should cause the rest point to shift back to the rest point determined in Step *A* or farther.

C. Place a 10-g. weight in the center of the right pan, and place a 10-g. weight successively toward the right, left, front, and back of the left pan, noting the rest point in each case. If in any case the rest point is different from that obtained with no weights on the pans, this difference should be overcome by addition of the 10-mg. weight to the lighter side.

D. Make a series of observations in which both weights are simultaneously shifted to off-center positions on their pans, both toward the outside, both toward the inside, one toward the outside, and the other toward the inside, both toward the back, and so on until all combinations have been checked. If in any case the rest point differs from that obtained with no weights on the pan the addition of the 10-mg. weight to the lighter side should overcome this difference.

A balance which does not meet the requirements of these tests must be adjusted.

4. *Rider and Graduated Beam Tests*—Determine the rest point for the balance with no weight on the pans. Now place on the left pan the 500-mg. test weight and move the rider to the 500-mg. point on the beam. Now determine the rest point. If it is different from the zero rest point, add a 6-mg. weight to the lighter side. This should bring the rest point back to its original position or farther. Repeat this test, using the 1-g. test weight and moving the rider to the 1-g. division on the beam. If the rest point is different it should be brought back at least to the zero rest point position by addition of 6 mg. to the lighter pan. If the balance does not meet this test, the weighbeam graduations or the rider must be corrected.

A suitable form for recording the results of periodic tests of prescription balances is shown in the accompanying test chart.

Prescription Balance Test Chart

Date of Test	Sensitivity Requirement No. of divisions rest point is shifted by 6 mg. (check if not at least 1 div.)		Arm Ratio 20 mg. should overcome rest point difference with 30 g. on each pan. Check if requirement is met	Shift Tests 10 mg. should overcome rest point difference. Check if requirement is met			Rider and Weighbeam Tests 6 mg. should overcome rest point difference. Check if requirement is met	
	No Load	10-g. Load		Right Weight Shifted	Left Weight Shifted	Both Weights Shifted	500-mg. Test	1-g. Test

Weights

Metric weights for use with a prescription balance should meet the National Bureau of Standards requirements for analytical weights. They should be kept in a special wooden or plastic box, and handled with forceps. *Apothecaries' weights* should have the same general (cylindrical) construction as metric weights. Coin-type weights are not recommended.

Test weights consisting of two 10-g., one 1-g., one 500-mg., one 20-mg., and one 10-mg. weights, adjusted to N.B.S. tolerances for analytical weights, should be used for testing the prescription balances. These weights should be kept in a tightly closed box and should be handled only with forceps.

Measuring Devices

Pharmaceutical devices for measuring volumes of liquids, including burets, pipets, and cylinders graduated either in metric or apothecary units should meet the standard specifications for glass volumetric apparatus described in Circular 602 of the National Bureau of Standards.* Conical graduates should meet the standard specifications described in Handbook 44, 3rd Edition, of the National Bureau of Standards.† Graduated medicine droppers should meet the specifications for pipets. An acceptable ungraduated medicine dropper should have a delivery end 3 mm. in external diameter, and be adjusted to deliver 20 drops of water, weighing 1 g., at a temperature of 15°. A tolerance of 10 percent below or 10 percent above the delivery specification is reasonable.

Selection and Use of Graduates—

Capacity—The capacity of a graduate is the designated volume, at the maximum graduation, that the graduate will contain or deliver, as indicated, at the specified temperature.

Cylindrical and Conical Graduates—The error in a measured volume caused by a deviation of ±1 mm., in reading the lower meniscus in a graduated cylinder remains constant along the height of the uniform column. The same deviation of ±1 mm. causes a progressively larger error in a conical graduate, the extent of the error being further dependent upon the angle of the flared sides to the perpendicular of the upright graduate. A deviation of ±1 mm. in the meniscus reading will cause an error of approximately 0.5 ml. in the measured volume at any mark on the uniform 100-ml. cylinder graduate. The same deviation of ±1 mm. can cause an error of 1.8 ml. at the 100-ml. mark on an acceptable 125-ml. (4-fluidounce) conical graduate.

A general rule for selection of a graduate for use is: Use the graduate with a capacity equal to or *just exceeding* the volume to be measured. Measurement of small volumes in large graduates tends to increase errors, because the larger diameter increases the volume error in a deviation of ±1 mm. from the mark. The relation of the volume error to the internal diameters of graduated cylinders is based upon the equation: $V = \pi r^2 h$. An acceptable 10-ml. cylinder with an internal diameter of 1.18 cm. holds 0.109 ml. in 1 mm. of the column. Reading 4.5 ml. in this graduate with a deviation of ±1 mm. from the mark causes an error of about ±2.5 per cent; while the same deviation in a volume of 2.2 ml. in the same graduate causes an error of about ±5 per cent. Minimum volumes that can be measured within certain limits of error in graduated cylinders of different capacities are incorporated in the design details of graduates in Handbook 44, 3rd Edition, of the National Bureau of Standards.

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* N.B.S. Circular 602 (April, 1959) is for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, DC 20402.

† N.B.S. Handbook 44, 3rd Edition (1965), is for sale by the above Office.

CLINICAL LABORATORY REAGENTS

In this Section, formulas are given for a selected group of clinical laboratory reagents that pharmacists may be requested to prepare from time to time. The reagent solutions are listed alphabetically, according to the common or usual name. In preparing these solutions, reagent grade chemicals of USP, NF, or other recognized quality should be used. For convenience, the biological staining solutions in this category are listed separately, beginning on page 956.

Benedict's Qualitative Reagent

Cupric Sulfate	17.3 g.
Sodium Citrate	173 g.
Monohydrated Sodium Carbonate	117 g.
Purified Water, a sufficient quantity,	
To make	1000 ml.

With the aid of heat dissolve the sodium citrate and the monohydrated sodium carbonate in about 700 ml. of purified water.

Filter through paper, if necessary. Dissolve the cupric sulfate in about 100 ml. of purified water, and slowly add this solution, with constant stirring, to the first solution. Cool the mixture and add enough purified water to make the product measure 1000 ml. The mixed solution is ready for use and does not deteriorate.

Do not use this reagent for Benedict's quantitative test.

Benzidine Test Reagent

Benzidine	10 g.
Glacial Acetic Acid	100 ml.

Add the benzidine to the glacial acetic acid, shake well until a saturated solution is obtained, and then filter or decant the clear supernatant solution. Keep in amber-colored bottles or in a dark place. Preferably prepare freshly for immediate use. This solution should never be used if it is more than 1 week old.

Bial's Test Reagent

Orcinol	1.5 g.
Ferric Chloride, 10% Solution	2.0 ml.
Hydrochloric Acid	500 ml.

Dissolve the orcinol in the hydrochloric acid and add the ferric chloride solution.

Bouin's Fluid

Formaldehyde Solution	25 ml.
Glacial Acetic Acid	5 ml.
Picric Acid	
Purified Water, each, a sufficient quantity.	

Add sufficient picric acid to purified water to make a saturated solution and maintain an excess of picric acid. Decant or filter, and to 75 ml. of clear saturated solution of picric acid add the formaldehyde solution and the glacial acetic acid and mix.

Exton's Test Reagent

Sulfosalicylic Acid	5.0 g.
Sodium Sulfate	20 g.
Purified Water, a sufficient quantity,	
To make	100 ml.

Dissolve the sodium sulfate in 75 ml. of purified water, add the sulfosalicylic acid, shake until dissolved, and then add sufficient purified water to make 100 ml.

Fehling's Qualitative Reagent

1. Cupric Sulfate	34.64 g.
Purified Water, a sufficient quantity,	
To make	500 ml.

Dissolve the cupric sulfate in the purified water.

2. Sodium Hydroxide	50 g.
Potassium Sodium Tartrate	173 g.
Purified Water, a sufficient quantity,	
To make	500 ml.

Dissolve the sodium hydroxide and the potassium sodium tartrate in the purified water.

Preserve the solutions separately in tight containers. Keep Solution 2 in a nonsoluble glass container with a paraffined glass stopper. Mix them in equal volumes when needed for use. The mixture tends to deteriorate.

Flemming's Fluid

Chromium Trioxide	750 mg.
Osmium Tetroxide	400 mg.
Glacial Acetic Acid	1.0 to 5.0 ml.
Purified Water, a sufficient quantity,	
To make	100 ml.

Dissolve the chromium trioxide in 75 ml. of purified water and the osmium tetroxide in 20 ml. of purified water, mix these solutions and add the glacial acetic acid. Prepare freshly as needed.

The amount of glacial acetic acid may be varied as desired. Because of the very irritating properties of osmium tetroxide, a sealed vial containing 1 g. of the reagent may be broken under 50 ml. of purified water to obtain the 20 ml. of osmium tetroxide solution. To preserve the remainder store in a tight container protected from light.

Formaldehyde Fixative Solution

Formaldehyde Solution, diluted with water as desired.

Gerhardt's Test Reagent

Ferric Chloride	10 g.
Purified Water, a sufficient quantity,	
To make	100 ml.

Dissolve the ferric chloride in the purified water.

Glycerin Jelly

Gelatin	40 g.
Arsenic Trioxide, Saturated Solution	200 ml.
Glycerin	120 ml.

Dissolve the gelatin in the aqueous solution of arsenic trioxide with the aid of gentle heat, add the glycerin, mix well, and cool.

Preserve in tight containers.

Haine's Qualitative Reagent

Cupric Sulfate	10 g.
Potassium Hydroxide	40 g.
Glycerin	90 ml.
Purified Water, a sufficient quantity,	
To make	1000 ml.

Dissolve the cupric sulfate in 400 ml. of purified water and add the glycerin; dissolve the potassium hydroxide in 500 ml. of purified water, and add slowly and with constant stirring to the cupric sulfate solution; then add sufficient purified water to make 1000 ml.

Hayem's Fluid

Mercury Bichloride	500 mg.
Sodium Chloride	1.0 g.
Sodium Sulfate	5.0 g.
Purified Water	200 ml.

Dissolve the salts in the purified water; filter. Refilter as necessary.

Lange, Legal, or Rothera Test Reagent

Sodium Nitroferricyanide	10 g.
Purified Water	30 ml.

Dissolve the sodium nitroferricyanide in the purified water. This solution should be freshly prepared just before use.

Ortho-Tolidine Test Reagent

Ortho-tolidine	4.0 g.
Glacial Acetic Acid	100 ml.

Dissolve the ortho-tolidine in the glacial acetic acid. This solution keeps for approximately 1 month.

Osmic Acid Solution

Osmium Tetroxide	1.0 g.
Purified Water	100 ml.

Dissolve the osmium tetroxide in the purified water. Because of the very irritating properties of osmium tetroxide, a sealed vial containing 1 g. of it may be broken under 100 ml. of purified water to obtain the solution.

Preserve in a tight container protected from light.

Oxalate Solutions—Blood Anticoagulants

1. Ammonium Oxalate or Sodium Oxalate	3.0 g.
Purified Water, a sufficient quantity,	
To make	100 ml.

Dissolve the ammonium oxalate or the sodium oxalate in the purified water. Note: Use 0.7 ml. of either solution for each 10 ml. of blood to be collected.

2. Lithium Oxalate or Potassium Oxalate	10.0 g.
Purified Water, a sufficient quantity,	
To make	100 ml.

Dissolve the lithium oxalate or the potassium oxalate in the purified water. Note: Use 0.1 to 0.15 ml. of the lithium oxalate solution, or 0.2 ml. of the potassium oxalate solution, for each 10 ml. of blood to be collected.

Note: In the selection of anticoagulant, care should be exercised to avoid interference with the chemical methods involved. No oxalate should be used if calcium is to be determined. Ammonium oxalate should not be used if ammonium, nonprotein nitrogen, urea, or protein is to be determined. Sodium or potassium oxalate should not be used if sodium, potassium, or base content is to be determined.

Ordinarily tubes or flasks to be used for collecting blood are prepared as follows: Pipet the proper amount of solution, as indicated above, into the tube or flask, spread about the inner surface of the lower portion of the container, and dry in an oven at a temperature not exceeding 80°. The dry salt will be deposited in a finely divided state upon the inner surface of the container.

Robert's Test Reagent

Nitric Acid	20 ml.
Magnesium Sulfate	57 g.
Purified Water	65 ml.

Dissolve the magnesium sulfate in the purified water, and add the nitric acid to the solution.

Schaudinn's Fluid

Mercury Bichloride	15 g.
Alcohol	100 ml.
Purified Water	200 ml.

Mix the alcohol and the purified water and dissolve the mercury bichloride in the solution.

Seliwanoff's Reaction Reagent

Resorcinol	50 mg.
Hydrochloric Acid	50 ml.
Purified Water	50 ml.

Mix the hydrochloric acid and the purified water; dissolve the resorcinol in the solution.

Topfer's Reagent

Dimethylaminoazobenzene	500 mg.
Alcohol	100 ml.

Dissolve the dimethylaminoazobenzene in the alcohol.

Zenker's Fluid

Mercury Bichloride	5.0 g.
Potassium Dichromate	2.5 ml.
Glacial Acetic Acid	5 ml.
Purified Water	100 ml.

With the aid of heat dissolve the mercury bichloride and the potassium dichromate in the purified water contained in a flask or an enameled pan. This is Zenker's Stock Solution.

Immediately before use, add the glacial acetic acid to the stock solution.

If *Formol-Zenker* is desired, mix 10 ml. of formaldehyde solution with 90 ml. of Zenker's Stock Solution.

INTERNATIONAL PHARMACOPOEIA

Almost eighty years after the initial efforts were made, the first volume of a pharmacopeia which attempts to set standards for drugs and preparations, and for pharmaceutic and diagnostic agents important to the promotion and protection of the health of all peoples, appeared in 1951. The second volume was published in 1955, and the first edition supplement was published in 1959. The second edition was published in 1967 under the title "Specifications for the Quality Control of Pharmaceutical Preparations." The standards included in the International Pharmacopoeia (Pharmacopoea Internationalis, Ph.I.) are not legally binding in any country unless the pharmacopeial authority of a country adopts it in part or in whole. The World Health Organization, under whose auspices the International Pharmacopoeia is published, hopes for the eventual inclusion of the provisions of the International Pharmacopoeia in the different national pharmacopeias.

Language

In the English printing of the International Pharmacopoeia, as in the French and Spanish printings, all official titles are in Latin. The second declension neuter endings are used almost exclusively for drug names. Latinized English is avoided in such instances as Kalii, Natrii, and Stibii for the respective potassium, sodium, and antimony compounds. Weights and measures are given only in the metric system.

Drugs of long-established therapeutic interest which are common to a number of national pharmacopeias are included, but the scope is not restricted to these. The text arrangement of the International Pharmacopoeia is very much like that of the National Formulary with the preface and general notices followed by the monographs of drugs and preparations. Appendices cover many of the general tests and processes, as in the United States Pharmacopeia and the National Formulary.

Monographs

Monographs in the International Pharmacopoeia follow the general style of the National Formulary. However, the name of the drug is mentioned in the rubric, definition, or tolerance statement at the beginning of the monograph and not again until the last statement in the monograph, which is the direction for storage.

Most of the tolerances allowed in the International Pharmacopoeia monographs are similar to those in the National Formulary. The articles for which monographs appear in the International Pharmacopoeia, Second Edition, and also in National Formulary XIII are listed in the Table which includes the official titles and condensed rubric statements.

Table of Comparisons of Ph.I. and NF XIII Articles Described in Both Compendia

Title		Strength	
Ph.I.	**NF**	**Ph.I.**	**NF**
Acidum Boricum	Boric Acid	99.0–100.5%	99.5–100.5% (dried basis)
Acidum Hydrochloricum Dilutum	Hydrochloric Acid Diluted	9.5–10.5% w/w	9.5–10.5% w/w
Acidum Nicotinicum	Niacin	99.5–100.5% (dried basis)	99.5–101.0% (dried basis)
Acidum Tartaricum	Tartaric Acid	99.5–100.5% (dried basis)	99.7–100.5% (dried basis)
Acidum Undecylenicum	Undecylenic Acid	95.0–103.0%	95.0–100.5%
Amodiaquini Hydrochloridum	Amodiaquine Hydrochloride	98.0–101.5% (anhydrous basis)	97.0–103.0% (anhydrous basis)
Amphetamini Sulfas	Amphetamine Sulfate	98.0–101.0% (dried basis)	98.0–100.5% (dried basis)
Amphetamini Sulfatis Compressi	Amphetamine Sulfate Tablets	90.0–110.0%	93.0–107.0%
Amyleni Hydras	Amylene Hydrate	...	...
Amylis Nitris	Amyl Nitrite	90.0–100.0%	95.0–105.0%

Table of Comparisons (continued)

Title		Strength	
Ph.I.	**NF**	**Ph.I.**	**NF**
Apomorphini Hydrochloridum	Apomorphine Hydrochloride	98.0–101.0% (dried basis)	98.5–100.5% (dried basis)
Bendroflumethiazidum	Bendroflumethiazide	98.0–102.0% (dried basis)	98.0–102.0% (anhydrous basis)
Bendroflumethiazidi Compressi	Bendroflumethiazide Tablets	92.5–107.5%	90.0–110.0%
Benzethonii Chloridum	Benzethonium Chloride	97.0–103.0% (dried basis)	97.0–103.0% (dried basis)
Benzethonii Chloridi Solutio	Benzethonium Chloride Solution	93.0–107.0% w/v	95.0–105.0%
Bismuthi Subnitras	Bismuth Subnitrate	70.5–73.5% Bi	NLT[a] 79.0% Bi_2O_3
Calcii Lactas	Calcium Lactate	98.0–101.0% (dried basis)	98.0–101.0% (dried basis)
Calcii Lactatis Compressi	Calcium Lactate Tablets	95.0–105.0%	94.0–106.0%
Calcii Para-Aminosalicylas	Calcium Aminosalicylate	98.0–101.0% (anhydrous basis)	98.0–100.5% (anhydrous basis)
Carbarsonum	Carbarsone	98.0–101.0% (dried basis)	97.5–101.0% (dried basis)
Carbarsoni Compressi	Carbarsone Tablets	93.0–107.0%	93.0–107.0%
Cetylpyridinii Chloridum	Cetylpyridinium Chloride	99.0–102.0%	99.0–102.0% (anhydrous basis)
Chlorcyclizini Hydrochloridum	Chlorcyclizine Hydrochloride	98.0–100.5% (dried basis)	98.0–100.5% (dried basis)
Chlorcyclizini Hydrochloridi Compressi	Chlorcyclizine Hydrochloride Tablets	93.0–107.0%	93.0–107.0%
Chloroformium Anesthesicum	Chloroform	98.05–99.5%	99.0–99.5%
Chlorothiazidum	Chlorothiazide	98.0–100.5% (dried basis)	98.0–100.5% (dried basis)
Chlorothiazidi Compressi	Chlorothiazide Tablets	95.0–105.0%	93.0–107.0%
Chlortetracyclini Hydrochloridum	Chlortetracycline Hydrochloride	NLT 900 IU[b]/mg. (dried basis)	NLT 90.0%
Codeinum	Codeine	99.0–100.5% (dried basis)	98.5–100.5% (dried basis)
Cresolum	Cresol	NLT 50.0% *m*-cresol	. . .
Dienestrolum	Dienestrol	98.0–100.5% (dried basis)	98.0–100.5% (dried basis)
Dienestroli Compressi	Dienestrol Tablets	90.0–110.0%	90.0–110.0%
Ephedrini Hydrochloridum	Ephedrine Hydrochloride	99.0–101.0% (dried basis)	98.0–100.5% (dried basis)
Estradioli Benzoas	Estradiol Benzoate	. . .	95.0–100.5% (dried basis)
Estradioli Benzoatis Injectio	Estradiol Benzoate Injection	90.0–115.0%	90.0–115.0%
Ether Vinylicus	Vinyl Ether	About 96% v/v	96.0–97.0%
Ethisteronum	Ethisterone	97.0–103.0% (dried basis)	98.0–102.0% (dried basis)
Ethisteroni Compressi	Ethisterone Tablets	90.0–110.0%	90.0–110.0%
Ethylis Aminobenzoas	Benzocaine	99.0–100.5% (dried basis)	98.0–101.0% (dried basis)
Ethylis Biscoumacetas	Ethyl Biscoumacetate	96.0–100.5% (dried basis)	97.0–101.0% (dried basis)
Ethylis Chloridum	Ethyl Chloride	. . .	99.5–100.5%
Ferrosi Gluconas	Ferrous Gluconate	95.0–100.5% (dried basis)	95.0–100.5% (dried basis)
Ferrosi Gluconatis Compressi	Ferrous Gluconate Tablets	90.0–110.0%	93.0–107.0%

Table of Comparisons (continued)

Title		Strength	
Ph.I.	NF	Ph.I.	NF
Glutethimidum	Glutethimide	99.0–100.5% (dried basis)	98.0–101.0% (dried basis)
Glutethimidi Compressi	Glutethimide Tablets	95.0–105.0%	95.0–105.0%
Hydralazini Hydrochloridum	Hydralazine Hydrochloride	98.0–102.0% (dried basis)	98.0–100.5% (dried basis)
Hydralazini Hydrochloridi Compressi	Hydralazine Hydrochloride Tablets	92.5–107.5%	95.0–105.0%
Hydrargyri Oxydum Flavum	Mercuric Oxide, Yellow	99.3–100.5% (dried basis)	99.5–100.5% (dried basis)
Hydroflumethiazidum	Hydroflumethiazide	98.0–102.0% (dried basis)	98.0–102.0% (anhydrous basis)
Hydroflumethiazidi Compressi	Hydroflumethiazide Tablets	92.0–107.5%	95.0–105.0%
Hydromorphoni Hydrochloridum	Hydromorphone Hydrochloride	98.5–101.0% (dried basis)	98.0–101.0% (dried basis)
Hydromorphoni Hydrochloridi Compressi	Hydromorphone Hydrochloride Tablets	90.0–110.0%	90.0–110.0%
Hydromorphoni Hydrochloridi Injectio	Hydromorphone Hydrochloride Injection	95.0–105.0%	95.0–105.0%
Lanatosidum C	Lanatoside C	90.0–102.0% (dried basis)	98.0–102.0% (dried basis)
Lanatosidi C Compressi	Lanatoside C Tablets	90.0–110.0%	90.0–110.0%
Menadionum	Menadione	98.5–100.5% (dried basis)	98.5–101.0% (dried basis)
Menadioni Compressi	Menadione Tablets	95.0–110.0%	95.0–110.0%
Menadioni Injectio	Menadione Injection	90.0–120.0%	90.0–120.0%
Methyltestosteronum	Methyltestosterone	96.0–102.0% (dried basis)	98.0–102.0% (dried basis)
Methyltestosteroni Compressi	Methyltestosterone Tablets	90.0–110.0%	90.0–110.0%
Methylthiouracilum	Methylthiouracil	98.0–100.5% (dried basis)	97.0–100.5% (dried basis)
Natrii Biphosphas	Sodium Biphosphate	98.0–100.5%	98.0–100.5% (anhydrous basis)
Nicethamidum	Nikethamide	98.0–100.5%	99.0–101.0% (anhydrous basis)
Nicethamidi Injectio	Nikethamide Injection	95.0–105.0%	95.0–105.0%
Noscapinum	Noscapine	98.5–100.5%	99.0–100.5% (anhydrous basis)
Novobiocinum Calcium	Calcium Novobiocin	NLT 850 IU/mg. (dried basis)	NLT 80% Novobiocin (dried basis)
Novobiocinum Natricum	Sodium Novobiocin	NLT 850 IU/mg. (dried basis)	NLT 80% Novobiocin (dried basis)
Oleum Jecoris Aselli	Cod Liver Oil	NLT 600 IU Vitamin A/g.	NLT 255 mcg. (850 USP Units) vitamin A and 2.125 mcg. (85 USP Units) vitamin D per g.
Papaverini Hydrochloridum	Papaverine Hydrochloride	99.0–100.5% (dried basis)	98.0–100.5% (dried basis)
Pentetrazolum	Pentylenetetrazol	98.0–101.0% (dried basis)	99.0–101.0% (dried basis)
Pentetrazoli Injectio	Pentylenetetrazol Injection	95.0–105.0%	95.0–105.0%
Phenazonum	Antipyrine	98.5–101.0%	99.0–100.5% (dried basis)

Table of Comparisons (continued)

Title		Strength	
Ph.I.	NF	Ph.I.	NF
Pheneticillum Kalicum	Potassium Phenethicillin	NLT 86.0% Total penicillins	NLT 90.0%
Pheneticillini Kalici Compressi	Potassium Phenethicillin Tablets	90.0–110.0%	NLT 85.0%
Phenindamini Tartras	Phenindamine Tartrate	98.5–101.0% (dried basis)	98.0–101.5% (dried basis)
Phenindamini Tartratis Compressi	Phenindamine Tartrate Tablets	92.5–107.5%	93.0–107.0%
Phentolamini Hydrochloridum	Phentolamine Hydrochloride	99.0–100.5% (dried basis)	98.0–100.5% (dried basis)
Phentolamini Hydrochloridi Compressi	Phentolamine Hydrochloride Tablets	90.0–110.0%	93.0–107.0%
Phenylhydrargyri Nitras	Phenylmercuric Nitrate	98.0–101.0% (dried basis)	Hg, 62.75–63.50%
Phthalylsulfathiazolum	Phthalylsulfathiazole	98.0–102.5% (dried basis)	98.0–100.5% (dried basis)
Picrotoxinum	Picrotoxin	. . .	. . .
Picrotoxini Injectio	Picrotoxin Injection	90.0–110.0%	90.0–110.0%
Progesteronum	Progesterone	97.0–103.0% (dried basis)	98.0–102.0% (dried basis)
Progesteroni Injectio	Progesterone Injection	90.0–110.0%	90.0–110.0%
Sennae Folium	Senna	. . .	. . .
Sulfamerazini Compressi	Sulfamerazine Tablets	95.0–105.0%	95.0–105.0%
Theophyllinum Natricum et Natrii Acetas	Theophylline Sodium Acetate	55.0–65.0% theophylline (anhydrous basis)	55.0–65.0% theophylline (anhydrous basis)
Tribromoethanolum	Tribromoethanol	99.0–100.5%	99.0–101.8% (dried basis)
Urethanum	Urethan	98.0–100.5%	99.0–101.0% (anhydrous basis)

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[a] NLT—Not less than; [b] IU—International Unit.

MEDICINE DROPPER

The National Formulary medicine dropper is 3 mm. in external diameter at its delivery end, and when held vertically delivers 20 drops of water, the total weight of which is between 900 mg. and 1.1 g.

In using a medicine dropper, one should keep in mind that few medicinal liquids have the same surface and flow characteristics as water, and therefore the size of drops varies materially from one preparation to another.

APPROXIMATE SOLUBILITIES OF SOME NATIONAL FORMULARY ARTICLES

The solubility data in the accompanying Table are intended as an aid to those who use these chemical substances in pharmaceutical practice, teaching, or research. The numerical values represent the approximate volume of a solvent required to dissolve 1 g. of a substance at 25°, unless another temperature is indicated. The absence of a value means that appropriate numerical solubility data are not available; it does not imply any particular degree of solubility.

Table of Approximate Solubilities of Some NF Articles

Solute (1 g.)	Name and Volume, in ml., of Solvent				
	Water	Alcohol	Chloroform	Ether	Other
Acetaminophen		10			Boiling water, 20; sodium hydroxide T.S., 15
Acetohexamide		230	210		
Acetophenazine Maleate	10	260	2850	6000	Acetone, 367; propylene glycol, 11
Acetyldigitoxin	6135	62.5	12	>10,000	
Acetyl Sulfisoxazole		176	35	1064	Methanol, 203
Alphaprodine Hydrochloride	2	7	3	4700	Acetone, 47
Alum	7				Boiling water, 0.3
Aluminum Chloride	0.9	4			
Alverine Citrate	120	35	500	9000	
Amantadine Hydrochloride	2.5	5.1	18		Polyethylene glycol 400, 70
Ambenonium Chloride	5	20	>1000	>1000	
Aminoacetic Acid	4	1254			Water at 50°, 2.6; at 75°, 1.9; at 100°, 1.5
Aminocaproic Acid	3				Methanol, 450
Ammonium Carbonate	4				
Amodiaquine Hydrochloride	25	78	>10,000	>10,000	Benzene, 10,000
Amphetamine Sulfate	9	500			
Anileridine	>10,000	2	1		
Anileridine Hydrochloride	5	80	>10,000	>10,000	
Anisindione	6250	380	11	400	Methanol, 300; dimethylformamide, 2.5
Antipyrine	<1	1.3	1	43	
Apomorphine Hydrochloride	50	50			Water at 80°, 20
Aprobarbital	250	4	28	7	Acetone, 3
Ascorbyl Palmitate	>1000	125	>1000	>1000	
Atropine	460	2	1	25	Water at 80°, 90
Bendroflumethiazide		23		200	
Benzethonium Chloride	<1	<1	<1	6000	
Benzocaine	2500	5	2	4	Almond oil or olive oil, 30–50
Benzphetamine Hydrochloride	1.5	1.5	1.5	1200	
Betamethasone	5300	65	325		Warm alcohol, 15; methanol, 3
Betamethasone Acetate	2000	9	16		
Betamethasone Sodium Phosphate	2	470	>10,000	>10,000	
Betamethasone Valerate	10,000	16	<10	400	
Bisacodyl	>10,000	210	2.5	275	
Boric Acid	18	18			Boiling water, 4; boiling alcohol, 6; glycerin, 4

Bromodiphenhydramine Hydrochloride	<1	2	2	3500	Isopropyl alcohol, 31
Brompheniramine Maleate	5	15	15		
Butalbital	625	3.4	25	5	
Butyl Aminobenzoate	7000				
Caffeine, Citrated					Warm water, 4
Calcium Aminosalicylate	7				
Calcium Benzoylpas	700				
Calcium Cyclamate	4	60			Propylene glycol, 1.5
Calcium Ipodate			2.6		
Calcium Lactate	20				
Calcium Novobiocin	250	30	1100	450	
Calcium Oxytetracycline	>1000	>1000	>1000	>1000	0.1 *N* Sodium hydroxide, 15
Calcium Saccharin	2.6	4.7			
Calcium Sulfate	375				Boiling water, 485
Carbarsone	1000 (60°)				
Carbetapentane Citrate	3.0	6.5	95	>1000	0.1 *N* Sodium hydroxide, 5
Carbinoxamine Maleate	<1	1.5	1.5	8300	
Carphenazine Maleate	600	400	>10,000	>10,000	
Cetylpyridinium Chloride	4.5	2.5	4.5		
Chloral Betaine	1	4	>10,000	>10,000	0.1 *N* Hydrochloric acid, 1; 0.1 *N* sodium hydroxide, 1
Chlorcyclizine Hydrochloride	2	11	4		
Chlordiazepoxide	>10,000	50	6250	134	
Chlormadinone Acetate		125	8	250	Methanol, 112
Chlormerodrin	60				Absolute alcohol, 300; methanol, 100
Chloroprocaine Hydrochloride	20	100			
Chlorothen Citrate	35				
Chlorotrianisene	4200	360	1.5	28	Methanol, 360; acetone, 7; benzene, 2.5
Chlorprothixene	1700	29	2	14	Acetone, 18
Chlortetracycline Hydrochloride	75	560			
Clidinium Bromide	25	40	6000	3500	
Cocaine	600	7	1	3.5	Olive oil, 12; liquid petrolatum, 80–100
Codeine	120	2	0.5	50	
Codeine Sulfate	30	1280			Water at 80°, 6.5
Cupric Sulfate	3	500			Boiling water, 0.5; glycerin, 3
Cyclopentamine Hydrochloride	1	2	1		Benzene, 25
Cyclothiazide		70			Methanol, 30
Cycrimine Hydrochloride	175	50	35		
Cyproheptadine Hydrochloride	275	35	26		Methanol, 1.5

Table of Approximate Solubilities of Some NF Articles (continued)

Solute (1 g.)	Name and Volume, in ml., of Solvent				
	Water	Alcohol	Chloroform	Ether	Other
Danthron		2000		500	Hot glacial acetic acid, 10
Dehydrocholic Acid		100	35	2174 (15°)	Acetic acid at 15°, 135; acetone at 15°, 129; benzene at 15°, 963; ethyl acetate at 15°, 135
Demeclocycline		200			Methanol, 40
Demeclocycline Hydrochloride	60				Methanol, 50
Denatonium Bromide	20	2.4	2.9	5000	
Desipramine Hydrochloride	12	14	3.5	>10,000	
Dexbrompheniramine Maleate	1.2	2.5	2	3000	
Dexchlorpheniramine Maleate	1.1	2	1.7	2500	
Dextroamphetamine Phosphate	20				
Dextromethorphan Hydrobromide	65				
Diazepam	333	16	2	39	
Dicyclomine Hydrochloride	13	5	2	770	Glacial acetic acid, 2
Diethylpropion Hydrochloride	0.5	3	3		
Dimethisoquin Hydrochloride	8	3	2		
Dimethisterone		3	0.7		
Diphemanil Methylsulfate	33	33	33		
Doxapram Hydrochloride	50				
Dromostanolone Propionate		30	2	20	
Dydrogesterone	>10,000	40	2	200	
Ephedrine	20	0.2			
Ephedrine Hydrochloride	3	14			
Erythromycin Estolate		20	10		Acetone, 15
Estradiol		28	435	150	
Estradiol Benzoate		97	4.6	146	
Estradiol Cypionate	>10,000	40	7	2800	
Estrone		250 (15°)	110 (15°)		Boiling alcohol, 50; boiling chloroform, 80; acetone at 50°, 50; boiling acetone, 33; boiling benzene, 145
Ethamivan	100				
Ethinamate	400	2.9			Hexane, 50; sesame oil, 143; 1,2-propylene glycol, 4.6
Ethoheptazine Citrate	30	140	>10,000	>10,000	
Ethyl Biscoumacetate	>10,000	410	3.0	215	Acetone, 20
Ethylmorphine Hydrochloride	10	25			
Ethyl Vanillin	100 (50°)	2			

Ferrous Gluconate	5				
Fluocinolone Acetonide	>1000	45	25	350	
Fluorometholone	>10,000	200	2200	>10,000	
Fluphenazine Enanthate		<1	<1	2	
Fluphenazine Hydrochloride	1.4	6.7			
Fluprednisolone	2500	100	400	350	
Flurandrenolide		72	10		Methanol, 25
Flurothyl	500				
Fluroxene	222				
Fructose		15			Methanol, 14
Fuchsin, Basic		15			
Gitalin	218	23.4	3.6	115	
Glutamic Acid Hydrochloride	3				
Glyceryl Guaiacolate	60–70				
Haloperidol	>10,000	60	15	200	
Hexylcaine Hydrochloride	17				
Hexylresorcinol	2000				
Hydralazine Hydrochloride	25	500			
Hydroflumethiazide	>5000	39	>5000	2500	
Hydromorphone Hydrochloride	3				
Hydroquinone	17	4	51	16.5	
Hydroxyzine Hydrochloride	1	4.5	13	>1000	
Hydroxyzine Pamoate	>1000	700	>1000	>1000	Dimethylformamide, 10; 1.0 *N* Sodium hydroxide, 3.5
Hyoscyamine Hydrobromide		2.5	1.7	2260	
Hyoscyamine Sulfate	0.5	5			
Indomethacin		50	30	40	
Iodoform		60	10	7.5	Boiling alcohol, 16; carbon disulfide, 3; glycerin, 80; olive oil, 34
Isocarboxazid	2000	83	2	58	
Isopropamide Iodide	50	10	5		
Isoxsuprine Hydrochloride	500	100	>10,000	>10,000	0.1 *N* Hydrochloric acid, 2500; 0.1 *N* sodium hydroxide, 100
Levopropoxyphene Napsylate		17	2		
Levorphanol Tartrate	50	120			
Menadione		60			Benzene, 10; vegetable oils, 50
Menadione Sodium Bisulfite	2				
Mepenzolate Bromide	112		627		Absolute alcohol, 121; methanol, 7.6
Mephobarbital	>1000	>1000	50	>1000	
Methacholine Chloride	1.2	1.7	2.1		
Methacycline Hydrochloride	100	300	>1000	>1000	0.1 *N* Sodium hydroxide, 25

Table of Approximate Solubilities of Some NF Articles (continued)

Solute (1 g.)	Name and Volume, in ml., of Solvent				Other
	Water	Alcohol	Chloroform	Ether	
Methapyrilene Hydrochloride	0.5	5	3		
Metharbital	830	23		40	
Methdilazine	>10,000	2	1	8	0.1 *N* Hydrochloric acid, 40; 0.1 *N* sodium hydroxide, >10,000
Methdilazine Hydrochloride	2	2	6	>10,000	0.1 *N* Hydrochloric acid, 1; 0.1 *N* sodium hydroxide, 1
Methenamine	1.5	12.5	10	320	
Methionine	30				Water at 0°, 55; at 50°, 16; at 75°, 9.5; at 100°, 5.7
Methocarbamol	40 (20°)				
Methotrimeprazine	10	10	2		Methanol, 10
Methscopolamine Bromide	6	80	>10,000	>10,000	
Methsuximide	350	3	<1	2	
Methyclothiazide	>10,000	92.5	>10,000	2703	
Methylprednisolone	10,000	100	800	800	
Methylprednisolone Acetate	1500	400	250	1500	
Methylprednisolone Sodium Succinate	1.5	12	>10,000	>10,000	
Methylthiouracil	150 (Boiling)				
Methyprylon	11	2	2	2	
Methysergide Maleate	200	165	3400	>10,000	
Nalidixic Acid	>1000	910	29	>1000	
Nandrolone Phenpropionate		2			
Niacin	60				
Nialamide	500	30	425	>1000	0.1 *N* Hydrochloric acid, 40
Nifuroxime	1000	25			
Nitrofurazone	4200	590			Propylene glycol, 350
Norethindrone Acetate	>10,000	10	<1	18	Dioxane, 2
Nortriptyline Hydrochloride	90	30	20		Methanol, 10
Noscapine		250	5	250	Glacial acetic acid, 2; acetone, 20; benzene, 31; petroleum ether, 4000; toluene, 40
Nylidrin Hydrochloride	65	40			
Oleandomycin Phosphate	2.2	3			
Orphenadrine Citrate	45	63	>10,000		0.1 *N* Hydrochloric acid, 2
Oxazepam	>10,000	220	270	2200	
Oxtriphylline	1				

Oxymetazoline Hydrochloride	6.7	3.6	862		
Oxymetholone	>10,000	40	5	82	Dioxane, 14
Oxymorphone Hydrochloride	4	100	>1000	>1000	Methanol, 25
Oxyphenbutazone	>10,000	1.5	4.0	15	
Oxyphencyclimine Hydrochloride	100	75	500	>1000	
Papaverine Hydrochloride	30	120			
Paramethasone Acetate			50		Methanol, 40
Pargyline Hydrochloride	0.6	5	7.2		
Paromomycin Sulfate	<1	>10,000	>10,000	>10,000	
Pectin	20				
Pentazocine	>1000	11	2	42	
Penthienate Bromide	5				
Perphenazine		7			Acetone, 13
Phenacaine Hydrochloride	50				
Phenindamine Tartrate	40	350			
Phenmetrazine Hydrochloride	0.4	2	2		
Phenolphthalein		15		100	
Phensuximide	210	11	<1	19	
Phentolamine Hydrochloride	50	100			
Phenylmercuric Acetate	180	22.5	6.8	200	
Phenylmercuric Nitrate	600				
Picrotoxin	350	13.5			Boiling water, 5; boiling alcohol, 3
Piminodine Esylate	>1000	6	2	>1000	
Pipobroman	228	35	4.8	526	
Polyethylene Glycol 1540	1		3		Absolute alcohol, 100
Polythiazide	>1000	150	175	>1000	
Potash, Sulfurated	2				
Potassium Acetate	0.5	3			Boiling water, 0.2
Potassium Citrate	1				Glycerin, 2.5
Potassium Gluconate	3				
Potassium Guaiacolsulfonate	7.5				
Potassium Phenethicillin	<10	59	331	>5000	
Potassium Sodium Tartrate	1				
Potassium Sorbate	4.5	35	>1000	>1000	
Potassium Warfarin	1.5	1.9	>10,000	>10,000	
Pramoxine Hydrochloride			35		
Prednisolone Succinate	4170	6.3	1064	248	
Prilocaine Hydrochloride	3.5	4.2	175		
Promazine Hydrochloride	3				

Table of Approximate Solubilities of Some NF Articles (continued)

Solute (1 g.)	Name and Volume, in ml., of Solvent				
	Water	Alcohol	Chloroform	Ether	Other
Propiomazine Hydrochloride	<1	6	2	>10,000	
Pseudoephedrine Hydrochloride	0.5	3.6	90.9	7000	
Pyrilamine Maleate	0.5	3	2		Absolute alcohol, 15
Pyrrobutamine Phosphate		20			Warm water, 10
Quinine Dihydrochloride	0.6	12			
Rescinnamine	>1000	500	8	>1000	
Rolitetracycline	1.1	200			
Salicylamide	500	15	100	35	Propylene glycol, 20
Selenium Sulfide			161	1667	
Sodium Acetate	0.8	19			Boiling water, 0.6
Sodium Butabarbital	2	7	7000	>10,000	
Sodium Cyclamate	5				Propylene glycol, 24
Sodium Dextrothyroxine	700	300			
Sodium Ipodate	<1	2			Dimethylacetamide, 2; dimethylformamide, 3.5; dimethylsulfoxide, 3.5
Sodium Novobiocin	2.3	19.5			
Sodium Phosphate	4				
Sodium Phosphate, Dried	8				
Sodium Propionate	1	24			Water at 100°, 0.65
Sodium Saccharin	1.5	50			
Sorbic Acid	1000	10	15	30	Absolute alcohol, 8; methanol, 8; propylene glycol, 19
Stanozolol	>1000	41	74	374	
Sucrose Octaacetate	1100	11			Acetone, 0.3; benzene, 0.6; toluene, 0.5
Sulfacetamide	140	15			Acetone, 7
Sulfadimethoxine		200			2 *N* Hydrochloric acid, 50
Sulfaethidole	>3000	75	1300	1700	Methanol, 51; acetone, 13; benzene, 2277
Sulfamethizole	2000	38	1888	1936	Acetone, 13
Sulfamethoxazole	3400	50	1000	1000	Carbon disulfide, 2 (slowly and usually incompletely)
Syrosingopine			4		Methanol, 200
Tartaric Acid	0.8	3		250	Boiling water, 0.5; methanol, 1.7
Terpin Hydrate	200	13	140	140	Boiling water, 35; boiling alcohol, 3
Testosterone			2	100	Absolute alcohol, 6
Tetracaine	>1000	5	2	2	
Tetrahydrozoline Hydrochloride	3.5	7.5	>1000	>1000	
Theophylline Sodium Acetate	25				

Theophylline Sodium Glycinate	6				
Thiethylperazine Maleate	1700	530	>10,000	>10,000	
Thihexinol Methylbromide	60	25	50	10,000	
Thimerosal	1	12			
Thioguanine		7700			
Tranylcypromine Sulfate	25				
Triacetin	14	1	1	1	
Triamcinolone Diacetate		13	80		Methanol, 40
Tribromoethanol	35				
Triclobisonium Chloride	2	2	4	540	
Tridihexethyl Chloride	3	3	2		
Triethylenemelamine	2.5	13	3.6		Methanol, 8; acetone, 9.5; benzene, 18
Trifluoperazine Hydrochloride	3.5	11	100		
Triflupromazine Hydrochloride	<1	<1	1.7		
Trimeprazine Tartrate	2	20	5	1800	
Trimethidinium Methosulfate	<1	<1	2	>10,000	
Trimethobenzamide Hydrochloride	2	59	67	720	
Trioxsalen		1150	84		Methylenedichloride, 43; 4-methyl-2-pentanone, 100
Triprolidine Hydrochloride	2.1	1.8	1	2000	
Troleandomycin		10			
Tromethamine	1.8	45.5	>10,000		
Tuaminoheptane Sulfate	105	53	3.5	30	Methanol, 10
Tybamate	2000	0.6	0.5	1	Propylene glycol, 2
Tyrothricin		15			
Urethan	0.5	1	1	2	Glycerin, 3; olive oil, 35
Valethamate Bromide	5	5	3		Glacial acetic acid, 5
Xylometazoline Hydrochloride	35				

STAINING SOLUTIONS

Dyes certified by the Biological Stain Commission* should always be used for preparing staining solutions. These dyes are designated as "Certified Biological," which indicates that they comply with certain chemical and functional specifications established by the Commission.

When alcohol is specified in the formulas for staining solutions, it is permissible to replace it with one of the specially denatured alcohols, such as formula 3 A, prepared by adding five gallons of methyl alcohol to one hundred gallons of ethyl alcohol.

Acid Fuchsin Solution

Acid Fuchsin	1.0 g.
Diluted Hydrochloric Acid	0.1 ml.
Purified Water	100 ml.

Add the diluted hydrochloric acid to the purified water and dissolve the acid fuchsin in the solution.

Alcoholic Eosin Solution

Ethyl Eosin	1.0 g.
Alcohol	100 ml.

Dissolve the ethyl eosin in the alcohol.

Aqueous Eosin Solution

Eosin Y	100 mg. to 1.0 g.
Purified Water	100 ml.

Dissolve the eosin Y in the purified water. Variation in the concentration of the solution is permitted for specific purposes.

Aqueous Methylene Blue Solution

Methylene Blue	1.0 g.
Purified Water	100 ml.

Dissolve the methylene blue in the purified water.

Basic Fuchsin Solution

Basic Fuchsin	60 mg.
Purified Water	100 ml.

Dissolve the basic fuchsin in the purified water.

Bismarck Brown Solution

Bismarck Brown Y	200 mg.
Purified Water	100 ml.

Heat the purified water and dissolve the bismarck brown in it by agitation.

Delafield's Hematoxylin Solution

Ammonium Alum	6.0 g.
Hematoxylin	400 mg.
Alcohol	2.5 ml.
Glycerin	10 ml.
Methanol	10 ml.
Purified Water	40 ml.

Dissolve the ammonium alum in the purified water and the hematoxylin in the alcohol; mix the two solutions. Expose the mixture to light and air in an unstoppered bottle for four days or longer, filter, and add the glycerin and the methanol to the filtrate. Allow this to stand in a well-stoppered container preferably for at least two months, and filter if necessary until the solution is clear. Dilute with water as desired before using.

Ehrlich's Aniline Gentian Violet Solution

Crystal Violet	1.2 g.
Aniline	2 ml.
Alcohol	12 ml.
Purified Water	98 ml.

Shake the aniline with the purified water, allow the mixture to stand several minutes and filter until clear. Dissolve the crystal violet in the alcohol. Mix the two solutions.

Giemsa's Staining Solution

Azure II-Eosin	3.0 g.
Azure II	800 mg.
Glycerin	250 g.
Methanol	250 g.

Mix the methanol and glycerin, warm to 60°, and dissolve the dyes in the mixture. Allow the mixture to stand for about 24 hours and then filter.

The dyes are sometimes combined and marketed in a dry form as Giemsa's Stain. A corresponding quantity of this may be substituted for the dyes.

Gram's Iodine Solution

Iodine	1.0 g.
Potassium Iodide	2.0 g.
Purified Water	300 ml.

Dissolve the iodine and potassium iodide in 5 ml. of purified water and mix this solution with the remainder of the water.

Heidenhain's Hematoxylin Solution

1. Ferric Ammonium Sulfate	3 g.
Purified Water	100 ml.

Dissolve the ferric ammonium sulfate in the purified water.

2. Hematoxylin	500 mg.
Purified Water	100 ml.

Dissolve the hematoxylin in the purified water. Allow the solution to stand in a well-stoppered container for 4 or 5 weeks and filter, if necessary.

Mix equal parts of the two solutions just before using as a stain.

Hematoxylin and Eosin Solution

1. Hematoxylin	1.0 g.
Purified Water	100 ml.

Dissolve the hematoxylin in the purified water. Allow the solution to stand in a well-stoppered container for 4 or 5 weeks and filter, if necessary.

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* Biological Stain Commission, University of Rochester Medical Center, 260 Crittenden Blvd., Rochester, NY 14620.

2. Aqueous Eosin Solution

Mix equal parts of the two solutions just before using as a stain.

Hucker's Gentian Violet Solution

Crystal Violet	2.0 g.
Ammonium Oxalate	800 mg.
Alcohol	20 ml.
Purified Water	80 ml.

Dissolve the crystal violet in the alcohol, and the ammonium oxalate in the purified water. Mix the two solutions and filter.

The concentration of crystal violet may be varied as desired. Twenty ml. of an alcohol solution of the dye is to be mixed with 80 ml. of an aqueous solution of the ammonium oxalate.

Iodine Water

Iodine,
Purified Water, each, a sufficient quantity.

Add iodine to purified water and shake repeatedly during 24 hours to obtain a saturated solution.

Loeffler's Alkaline Methylene Blue Solution

Methylene Blue	300 mg.
Alcohol	30 ml.
Potassium Hydroxide (1 in 10,000 solution)	100 ml.

Dissolve the methylene blue in the alcohol, add the potassium hydroxide solution, and mix.

Mallory's Stain

1. Acid Fuchsin	500 mg.
Purified Water	100 ml.

Dissolve the acid fuchsin in the purified water.

2. Aniline Blue, Water-soluble	500 mg.
Orange G	2.0 g.
Phosphotungstic Acid	1.0 g.
Purified Water	100 ml.

Dissolve the aniline blue, orange G, and phosphotungstic acid in the purified water.

Mayer's Hemalum Solution

Hematein	1 g.
Alum	50 g.
Alcohol	50 ml.
Water	1000 ml.

Dissolve the hematein in the alcohol, the alum in the water, and add the hematein solution to the alum solution slowly with constant stirring. Allow this to stand for several days and, before using, filter until the solution is clear.

Nicollé Carbol-Gentian Violet Solution

Crystal Violet	1.0 g.
Phenol	1.0 g.
Alcohol	10 ml.
Purified Water	100 ml.

Dissolve the crystal violet in the alcohol, and the phenol in the purified water. Mix the solutions and filter.

Neisser's Staining Solution

Methylene Blue	100 mg.
Alcohol	2.0 ml.
Glacial Acetic Acid	5.0 ml.
Purified Water, a sufficient quantity,	
To make	100 ml.

Dissolve the methylene blue in purified water, add the alcohol, glacial acetic acid, and sufficient water to make 100 ml.

Neutral Red Solution

Neutral Red	1.0 g.
Purified Water	100 ml.

Dissolve the neutral red in the purified water.

Pappenheim's Methyl Green-Pyronin Solution

Methyl Green	1.00 g.
Pyronin Y	250 mg.
Phenol	2.0 g.
Glycerin	20 ml.
Alcohol	5 ml.
Purified Water	100 ml.

Dissolve the methyl green in the alcohol. Mix the glycerin and purified water and dissolve the pyronin Y and phenol in the mixture. Mix the two solutions and filter.

Safranin Solution

Safranin O	250 mg.
Alcohol	10 ml.
Purified Water	100 ml.

Dissolve the safranin O in the alcohol, add the purified water, and mix.

Stirling's Gentian Violet Solution

Crystal Violet	5.0 g.
Aniline	2.0 ml.
Alcohol	10 ml.
Purified Water	88 ml.

Mix the aniline with the alcohol, dissolve the crystal violet in the mixture, add the purified water, mix well, let stand for 24 hours or longer, and filter.

Wright's Staining Solution

Methylene Blue	900 mg.
Sodium Bicarbonate	500 mg.
Eosin Y	1.0 g.
Purified Water	600 ml.

Methanol, a sufficient quantity.

Dissolve the methylene blue and sodium bicarbonate in 100 ml. of purified water, place in container so that the depth of the solution is not more than 6 cm., and heat in a steam sterilizer at 100° for 1 hour. Cool the solution and filter. Dissolve the eosin Y in 500 ml. of purified water. Add this to the methylene blue solution, mix thoroughly, filter, and dry the precipitate. This is Wright's stain.

For use dissolve 100 mg. of Wright's stain in 60 ml. of methanol, allow the solution to stand for a day or two, and filter.

Wright's stain is marketed in a dry form and a corresponding quantity of this may be used in preparing the solution.

Ziehl-Neelsen Carbol-Fuchsin Solution

Basic Fuchsin	300	mg.
Alcohol	10	ml.
Liquefied Phenol	5	ml.
Purified Water	95	ml.

Dissolve the basic fuchsin in the alcohol, and the liquefied phenol in the purified water. Mix the solutions.

STERILIZATION*

The method of attaining sterility in a pharmaceutical product is determined largely by the character of the product. The preparation of sterile products requires intimate knowledge of the equipment being used and of the stability of the product being processed. The sterilization process requires vigilant supervision of equipment and procedures by personnel well trained in devising and applying methods for attaining sterility, and adequate proof of the effectiveness of procedures used.

Solids

Soluble solids distributed in sealed containers for the extemporaneous preparation of injectable solutions are often sterilized and packaged aseptically unless the product is capable of being heated sufficiently in the dry state to render it sterile. In the latter case, the necessary processing must be adapted to the individual product. The customary autoclaving temperatures alone are not adequate for sterilization of sealed containers of nonaqueous contents.

Purified cotton, gauze, and surgical dressings are usually sterilized in an autoclave with saturated steam. In small packages loosely packed and wrapped in muslin or paper, these dressings may be sterilized at 121° in 30 minutes provided the air has been eliminated from the dressings and the sterilizing chamber by creating a suitable vacuum within the chamber before bringing the contents up to sterilizing temperature. In the commercial sterilization of large quantities of dressings, manufacturers have developed elaborate procedures in which repeated applications of vacuum and saturated steam are required to exhaust all of the air and to assure complete penetration of the contents by the moist heat. In such large-scale operations, thermocouples connected to suitable recording devices are used throughout the sterilizing chamber. These articles may be sterilized by proper use of ethylene oxide gas. For sterilization on a small scale, as in hospitals, "sterilization detectors" are placed within the packages of dressings. Such controls should be capable not only of indicating the attainment of an effective sterilization temperature, but also of giving an indication of the duration of that temperature.

The variety of materials from which sutures are derived calls for a corresponding variety of sterilization procedures, so that a detailed exposition of the latter herein would be impracticable. Methods have been developed empirically for each type of suture through trial runs of artificially contaminated products with subsequent tests for sterility. Certain forms of electronic sterilization also are used.

Assemblies of rubber tubing for the collection, handling, or administration of blood plasma, or the administration of infusion solutions, are customarily sterilized in an autoclave with saturated steam at a temperature of 121° for at least 20 minutes. If assemblies are made of plastic material which will not withstand the autoclave temperatures, sterilization may be effected by the use of ethylene oxide gas. The latter is frequently diluted, in the interests of safe handling, with nine parts of carbon dioxide or other inert, nonflammable gas.

The effectiveness of the procedure must be thoroughly demonstrated by repeated tests with assemblies which have been contaminated with resistant spores, and then subjected to treatment and finally to sterility testing. (See *Sterility Tests*, page 874).

Ethylene Oxide Sterilization—Some types of materials can be sterilized more efficiently by exposure to ethylene oxide gas than by the use of heat or other means. The pure gas is highly flammable when mixed with air but can be employed safely when properly diluted with an inert gas such as carbon dioxide or a suitable fluorinated hydrocarbon. Such mixtures are available commercially.

Sterilization with ethylene oxide requires specialized, but not necessarily elaborate, equipment designed for the particular purpose. Commercial units are available for the treatment of a large variety of pharmaceutical and other products. The efficacy of any procedure for the sterilization of pharmaceutical products by ethylene oxide should be tested thoroughly by the inclusion of items contaminated with spores of known microorganisms in representative locations in typical sterilizer loads and by subsequent demonstration that these microorganisms have not survived the treatment. Greater precautions are needed for this system of sterilization, since the conditions of time, temperature, gas concentration, humidity and other variables are such that the reliability of the process is not so firmly established as one involving autoclaving or dry-heat sterilization.

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* Note: All temperatures herein specified are in centigrade (Celsius) degrees and, with respect to autoclaves, generally mean the exhaust line temperatures.

Liquids

Heat Sterilization in Final Containers—Application of an effective process to destroy microorganisms in products packaged in their final containers has obvious advantages over procedures requiring the aseptic handling and filling of sterilized bulk materials. Most aqueous injections and solutions may be sterilized in the final container at suitable temperatures by the use of saturated steam under pressure in an autoclave.

Aqueous Injections—The characteristics of the injection determine the degree of heat and the duration of the exposure that may be applied; and the size of the container and the wall-thickness of the glass determine the time required for the solution within the container to attain the sterilizing temperature.

A solution that is sterilized by heating to 121° for 3 to 5 minutes when packaged in 50-ml. thin-walled ampuls requires from 6 to 8 minutes to reach this temperature after the thermometer in the steam discharge line registers 121°, whereas when packaged in 1000-ml. thick-walled glass bottles it requires 20 minutes or more after the thermometer registers 121°.

Autoclaves that come up to pressure quickly and can quickly be brought down to room pressure greatly facilitate sterilizing labile compounds that are damaged by prolonged heating. Some injections, such as *Sodium Chloride Injection*, may be subjected to a high temperature for prolonged periods with no decomposition, whereas *Dextrose Injection*, for example, must be brought quickly to sterilization temperature and then cooled quickly to avoid breakdown of some of the dextrose. Some solutions are sterilized at autoclave temperatures lower than 121° by prolonging the period of heating.

It is important that sterilization be controlled by a thermometer in the steam discharge line. The use of a recording thermometer is desirable and advantageous to provide a permanent record of the sterilization cycle.

It is desirable to check the heat distribution, particularly in new or remodeled autoclaves or after changes in the loading conditions, by placing suitable devices to register the temperatures attained on different horizontal and vertical planes of the sterilizing chamber. For this purpose, recording thermocouples sealed into representative containers of the preparation to be sterilized are preferred.

The personnel in charge of the sterilization of injections should be responsible for the procedures used by the technicians who operate the autoclave.

Many injections are solutions of drugs which are bactericidal *per se* or contain active bacteriostatic substances and may be sterilized through the combined action of heat and the bacteriostatic substance by exposing the filled containers to temperatures below 121°. However, the processing of injections at lower temperatures or for shorter durations than those generally recognized to be adequate for destruction of resistant spores involves a definite risk that the final product will not in fact be sterile. Such processes cannot be employed safely unless the efficacy of a given process for the destruction of thermo-resistant spores in the specified product has been demonstrated experimentally.

The "fractional sterilization" process, although effective for the sterilization of some culture media, is seldom satisfactory for solutions, containing non-nutritive material, inasmuch as bacterial spores may not germinate in them during the periods between heat treatment.

Nonaqueous Injections—Nonaqueous injections in sealed containers may fail to be sterilized at the customary temperatures of an autoclave, since in the absence of water vapor within the container the processing is only the equivalent of dry-heat sterilization. The process should be selected only on the basis of previously demonstrated adequacy to sterilize representative samples of such products, which have been inoculated with thermo-resistant spores.

Sterilization by Filtration—Injections that decompose at temperatures required to kill microorganisms must be sterilized in some other manner, such as by filtering through bacteria-retaining filters, and subsequently must be filled aseptically into sterile containers and sealed with sterile closures.

The candle-type of filter usually is made of unglazed porcelain or infusorial earth with binders of clay and asbestos. Available also are other types consisting of candles or disks of sintered-glass or stainless steel, and pads or disks of asbestos or cellulosic material. The solutions are forced through such filters with either negative or positive pressure and filled into sterile containers. Excessive positive pressures and leakage of air in negative pressure equipment should be avoided, since any leakage of air risks contamination. In selecting a filter, it must be kept in mind that the solution may react with some component of the filter, or some active medicament or bacteriostatic agent may be adsorbed on the filter and removed from solution. During filtration at room temperature over prolonged periods, the filter should be changed occasionally, since colonies of microorganisms may become well enough established in the filter pores to contaminate the effluent.

Sterilization by Irradiation—Techniques are available for the sterilization of some types of pharmaceutical products by gamma rays and by cathode rays, but the application of such techniques is limited because of the highly specialized equipment required and the effects of irradiation on products and their containers.

Sterilization of Containers—Empty containers for injections and glassware used for preparing and filling sterile solutions usually are sterilized by dry heat at 170° for 2 hours. Rubber closures are sterilized preferably with moist heat in an autoclave at 121° for 15 to 20 minutes. Vials and closures are packed in containers suitable for maintaining sterility until removed for use. If such containers are not hermetically sealed, "breathing" occurs with fluctuations in room temperature, and they should be used within a few days or be re-sterilized.

Aseptic Filling Areas—The principal purpose of aseptic filling is to avoid contaminating the injections which have already been rendered sterile.

Conceivably, microorganisms may float freely in the air, but more often they are found in association with dust particles and moisture droplets. From a practical standpoint, the removal of particles and droplets from the atmosphere of a working area usually so reduces the microbial content that it no longer constitutes a hazard to aseptic filling.

For minimizing the microbial count in the air of the so-called "dust-free rooms," various laboratories make use of filtered air, electrostatic precipitating devices, banks of ultraviolet lights, or combinations of these devices. Anterooms or vestibules are advantageous and the maintenance of positive air pressure in the filling areas is helpful to prevent an inrush of outside air when doors are opened.

To protect filling operations against droplet contamination from the breath of operators and their attendants, some laboratories require the use of masks, along with sterile gowns and coverings for the hair. Greater reliance, however, may be placed on conducting the filling operation under hoods or shields. The control of contamination brought in on shoes and trucks presents problems peculiar to each plant. Aseptic areas should not be open to visitors.

Control Checks on Aseptic Filling Rooms—In aseptic filling operations or in filling those products which are subjected to the so-called "marginal sterilization methods," it is important that the supervising personnel have some measure of the effectiveness of the precautionary procedures used to minimize the changes of microbial contamination. A method commonly used is the determination of the number of microbial colonies which develop on incubated plates of sterile, highly nutritive agar culture medium which have been exposed within the working areas during the filling operation.

The number and types of microorganisms found may suggest the source of contamination. Any general appraisal of the adequacy of the protective system should be based on the record of plate counts over a period of weeks or months.

A satisfactory positive general check on the entire filling operation may be had by processing under routine operating conditions the equivalent of a representative lot of containers, filling them with sterile thioglycollate medium or any other good culture medium, and then incubating the entire lot. A comprehensive sterility test such as this is not subject to the criticism of a test conducted solely on representative samples of filled containers of Injections. Records established by conducting this test at intervals are a valuable index to the confidence that may be placed in the procedure and are an important adjunct to the results of sterility tests on the finished product.

General Maintenance in Aseptic Areas—One of the most important aspects in the control of environmental contamination in filling rooms is the everyday janitorial care and maintenance of the aseptic areas. Ideally, the cleaning and maintenance should be done after the end of the day's work so that the rooms are unoccupied for some time, preferably overnight, before a new filling operation begins.

TEASPOON

Agreement has not been reached on a standard official teaspoon, in spite of the need for such a standard measure in connection with compounding and labeling liquid medicines. For household purposes, an American Standard Teaspoon has been established by the American Standards Association† as containing 4.93 ± 0.24 ml. In view of the almost universal practice of employing teaspoons ordinarily available in the household for the administration of medicine, the teaspoon may be regarded as representing 5 ml.

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† USA Standards Institute, 70 E. 45th St., New York, NY 10017.

It must be kept in mind that the actual volume delivered by a teaspoon of any given liquid is related to the latter's viscosity and surface tension, among other influencing factors.

Household units are usually used to advise the patient of size of the dose. Fifteen milliliters should be considered 1 tablespoonful; 10 ml., 1 desertspoonful; and 5 ml., 1 teaspoonful. Doses of less than 5 ml. are frequently stated as fractions of a teaspoonful or in drops. To ensure greater accuracy, it is preferable that these small quantities be dispensed equipped with suitable graduated droppers, usually graduated in ml. or fractions thereof, although dropper pipets in prepackaged preparations may be graduated in terms of mg. of that specific drug.

TITLES AND OTHER DESIGNATIONS

While the NF monograph titles are legally recognized as the only designations for use in labeling the articles to which they apply, many of the articles have been known by other nonproprietary¶ names. Some of these appeared in the monographs of NF XI and earlier revisions as synonyms for the official titles. Their inclusion in the accompanying list of Former Common Names, Titles, or Synonyms of Articles in NF XIII does not constitute sanction for their use, since they are listed here solely for reference purposes.

In cooperation with the USAN Council (see *General Principles*, page 1), the NF Board adopts the U.S. Adopted Name, if any, as the title for any compound that attains National Formulary recognition.

A nonproprietary name of a drug serves numerous and varied purposes, its principal function being to identify the substance to which it applies by means of a designation that may be used without restriction by the professional and lay public. Teaching in pharmacy and medicine requires a common designation, especially for a drug that is available from several sources; nonproprietary names facilitate communication among physicians; nonproprietary names must be used as the titles of the articles recognized by official drug compendia; a nonproprietary name is essential to the pharmaceutical manufacturer as a means of protecting trademark rights in the brand name for the article concerned; and, finally, the manufacturer is obliged by federal law to include the respective nonproprietary name in advertising, labeling, and brochures.

The accompanying list of Former Common Names, Titles, or Synonyms of Articles in NF XIII includes most of the NF synonyms, including popular or abbreviated designations, that appeared in the monographs of earlier revisions. A number of NF title changes also are reflected in the list.

Former Common Names, Titles, or Synonyms of Articles in NF XIII†

Former Name	NF XIII Title
p-Acetamidophenol	Acetaminophen
Acetic Ether	Ethyl Acetate
Acetyl-β-methylcholine Bromide	Methacholine Bromide
Acetyl-β-methylcholine Chloride	Methacholine Chloride
Acetylsalicylate Aluminum	Aluminum Aspirin
Acetylsalicylic Acid Capsules	Aspirin Capsules
Acetylsalicylic Acid, Acetophenetidin and Caffeine Tablets	Aspirin, Phenacetin and Caffeine Tablets
Alcohol Rubbing Compound	Rubbing Alcohol
Algin	Sodium Alginate
Allylisopropylmalonylurea	Aprobarbital
dl-Alpha Tocopherol*	Vitamin E
d-Alpha Tocopherol Acetate	Vitamin E
d-Alpha Tocopherol Acetate Concentrate	Vitamin E
dl-Alpha Tocopherol Acetate	Vitamin E
d-Alpha Tocopherol Acid Succinate	Vitamin E
d-Alpha Tocopheryl Acetate*	Vitamin E
d-Alpha Tocopheryl Acetate Concentrate*	Vitamin E
dl-Alpha Tocopheryl Acetate*	Vitamin E

¶ With reference to drug nomenclature, the term "generic" has been widely misused in place of the more accurate and descriptive term "nonproprietary." Used in the correct sense, "generic names" refers to names relating to classes or genera of drugs; e.g., the generic name Vitamin D applies to at least two compounds that exhibit antirachitic activity.

Names, Titles, Synonyms (continued)

Former Name	NF XIII Title
d-Alpha Tocopheryl Acid Succinate*	Vitamin E
Aluminum Acetylsalicylate	Aluminum Aspirin
2-Aminoheptane Sulfate	Tuaminoheptane Sulfate
Ammonium Ichthosulfonate	Ichthammol
Anhydrohydroxyprogesterone	Ethisterone
1,8,9-Anthratriol	Anthralin
APC Tablets	Aspirin, Phenacetin and Caffeine Tablets
Apricot Kernel Oil	Persic Oil
Aqua Rosae Fortior	Stronger Rose Water
Aromatic Yerba Santa Syrup	Aromatic Eriodictyon Syrup
Basic Aluminum Glycinate	Dihydroxyaluminum Aminoacetate
Basic Bismuth Nitrate	Bismuth Subnitrate
Beeswax	Yellow Wax
Beta-estradiol Benzoate	Estradiol Benzoate
Bismuth Cream	Milk of Bismuth
Bismuth Magma*	Milk of Bismuth
Bromethol*	Tribromoethanol Solution
Burnt Sugar Coloring	Caramel
Cade Oil	Juniper Tar
Caraway Seed	Caraway
Cascara Sagrada Extract Tablets	Cascara Tablets
Castellani's Paint	Carbol-Fuchsin Solution
Chloromethapyrilene Citrate	Chlorothen Citrate
Chrysazin	Danthron
Cocculin	Picrotoxin
Colophony	Rosin
Compound Calcium Cyclamate Solution	Calcium Cyclamate and Calcium Saccharin Solution
Compound Calcium Cyclamate Tablets	Calcium Cyclamate and Calcium Saccharin Tablets
Compound Cresol Solution	Saponated Cresol Solution
Compound Sodium Cyclamate Solution	Sodium Cyclamate and Sodium Saccharin Solution
Compound Sodium Cyclamate Tablets	Sodium Cyclamate and Sodium Saccharin Tablets
Darrow's Solution	Lactated Potassic Saline Injection
Demethylchlortetracycline for Oral Suspension*	Demeclocycline for Oral Suspension
Demethylchlortetracycline Syrup*	Demeclocycline Oral Suspension
Demethylchlortetracycline Hydrochloride*	Demeclocycline Hydrochloride
Demethylchlortetracycline Hydrochloride Capsules*	Demeclocycline Hydrochloride Capsules
Deoxycorticosterone Trimethylacetate	Desoxycorticosterone Pivalate
Desoxycorticosterone Trimethylacetate	Desoxycorticosterone Pivalate
Dibasic Sodium Phosphate	Sodium Phosphate
Dicumarol Capsules	Bishydroxycoumarin Capsules
Dihydromorphinone Hydrochloride**	Hydromorphone Hydrochloride
Dihydromorphinone Hydrochloride Injection	Hydromorphone Hydrochloride Injection
Dihydromorphinone Hydrochloride Tablets	Hydromorphone Hydrochloride Tablets
Dihydrotheelin	Estradiol
1,8-Dihydroxyanthranol	Anthralin
l-3,4-Dihydroxynorephedrine	Levonordefrin
Diodone Injection	Iodopyracet Injection
Diphenylacetylindandione	Diphenadione
Divinyl Oxide	Vinyl Ether
Dry Yeast	Dried Yeast
Dwarf Pine Needle Oil	Pine Needle Oil
Estradiol Injection, Aqueous*	Estradiol Suspension, Sterile
Estradiol Cyclopentylpropionate	Estradiol Cypionate
Estradiol Cyclopentylpropionate Injection	Estradiol Cypionate Injection
Ethyl Aminobenzoate	Benzocaine
Ethyl Aminobenzoate Ointment	Benzocaine Ointment
Expressed Almond Oil	Almond Oil
Exsiccated Sodium Phosphate*	Dried Sodium Phosphate

Names, Titles, Synonyms (continued)

Former Name	NF XIII Title
Flowers of Sulfur	Sublimed Sulfur
D-Fructose	Fructose
Furandrenolone Acetonide	Furandrenolide
Glycine	Aminoacetic Acid
Glycocoll	Aminoacetic Acid
Hexamethylenamine	Methenamine
Iodine Swabs	Iodine Ampuls
Isoamyl Nitrite	Amyl Nitrite
Iso-Elixir	Iso-Alcoholic Elixir
Isopropanol	Isopropyl Alcohol
Isopropanol Rubbing Compound	Isopropyl Rubbing Alcohol
Isopropyl Alcohol Rubbing Compound	Isopropyl Rubbing Alcohol
Lassar's Zinc Paste with Salicylic Acid	Zinc Oxide Paste with Salicylic Acid
Lavender Flowers Oil	Lavender Oil
Levulose	Fructose
Light Liquid Paraffin	Light Mineral Oil
Light Liquid Petrolatum	Light Mineral Oil
Light White Mineral Oil	Light Mineral Oil
Magnesium Phosphate, Tribasic*	Magnesium Phosphate
Medicinal Soft Soap	Green Soap
Medicinal Soft Soap Liniment	Green Soap Tincture
Menaphthone	Menadione**
Menaphthone Sodium Bisulfite	Menadione Sodium Bisulfite
Mercuric Oxide, Yellow, Ointment*	Mercuric Oxide, Yellow, Ophthalmic Ointment
Methenamine and Sodium Acid Phosphate Tablets	Methenamine and Sodium Biphosphate Tablets
DL-Methionine	Methionine
Mild Protargin	Mild Silver Protein
Mixed Tocopherols Concentrate	Vitamin E
Modified Dakin's Solution	Diluted Sodium Hypochlorite Solution
Monobasic Dextro-amphetamine Phosphate	Dextroamphetamine Phosphate
Monobenzyl Ether of Hydroquinone	Monobenzone
Monostearin	Glyceryl Monostearate
Narcotine	Noscapine**
Neroli Oil	Orange Flower Oil
Nicotinic Acid	Niacin
Nicotinic Acid Injection	Niacin Injection
Nicotinic Acid Tablets	Niacin Tablets
Nitrofurazone Soluble Dressing	Nitrofurazone Ointment
Nutmeg Oil	Myristica Oil
Octylphenoxy Polyethoxyethanol*	Octoxynol
Otto of Rose	Rose Oil
Peach Kernel Oil	Persic Oil
Peru Balsam	Peruvian Balsam
Petrolatum Emulsion, Liquid*	Mineral Oil Emulsion
Petrolatum, Light Liquid*	Light Mineral Oil
Petroleum Jelly	Petrolatum
Phenazone	Antipyrine
Phenethyl Alcohol	Phenylethyl Alcohol
Phenylcarbinol	Benzyl Alcohol
Pituitary Solution	Posterior Pituitary Injection**
Pix Liquida	Pine Tar
Pix Pini	Pine Tar
Plantain Seed	Plantago Seed
Polyethylene Glycol 1300–1600	Polyethylene Glycol 1540
Polyvinylpyrrolidone	Povidone
Posterior Pituitary Solution	Posterior Pituitary Injection**
Precipitated Calcium Phosphate	Tribasic Calcium Phosphate
Pregneninolone	Ethisterone
Procaine Penicillin and Buffered Penicillin for Aqueous Injection*	Procaine Penicillin G and Sodium Penicillin G for Injection
Propellant 11	Trichloromonofluoromethane
Propellant 12	Dichlorodifluoromethane

Names, Titles, Synonyms (continued)

Former Name	NF XIII Title
Propellant 114	Dichlorotetrafluoroethane
Propylene Glycol Ether of Methylcellulose	Hydroxypropyl Methylcellulose
Psyllium Seed	Plantago Seed
Racemic Amphetamine Sulfate	Amphetamine Sulfate
Radiocyanocobalamin Solution	Cyanocobalamin Co 60 Solution**
Resorcin Acetate	Resorcinol Monoacetate
Rhamnus Purshiana Extract	Cascara Sagrada Extract
Rhamnus Purshiana Fluidextract	Cascara Sagrada Fluidextract
Rochelle Salt	Potassium Sodium Tartrate
Saigon Cinnamon	Cinnamon
Saturated Potassium Iodide Solution	Potassium Iodide Solution
Selenium Disulfide	Selenium Sulfide**
Senna Leaves	Senna
Sodium Acid Phosphate	Sodium Biphosphate
Soft Soap	Green Soap
Soft Soap Liniment	Green Soap Tincture
Soluble Gluside	Sodium Saccharin
Soluble Saccharin	Sodium Saccharin
Soluble Saccharin Tablets	Sodium Saccharin Tablets
Sterile Desoxycorticosterone Trimethylacetate Suspension	Sterile Desoxycorticosterone Pivalate Suspension
Sterile Procaine Penicillin G and Buffered Crystalline Penicillin G for Suspension	Procaine Penicillin G and Sodium Penicillin G for Injection
Stronger Ammonium Hydroxide Solution	Strong Ammonia Solution
Sulfamethizole Suspension*	Sulfamethizole Oral Suspension
Sweet Almond Oil	Almond Oil
Syrup of Tolu	Tolu Balsam Syrup
Syrupus Corrigens	Aromatic Eriodictyon Syrup
Terpinol	Terpin Hydrate
Tertiary Amyl Alcohol	Amylene Hydrate
Tolu Tincture	Tolu Balsam Tincture
Triacetyloleandomycin*	Troleandomycin
Triacetyloleandomycin Capsules*	Troleandomycin Capsules
Tri-*p*-anisylchloroethylene	Chlorotrianisene
Urethane	Urethan
Vanilla Bean	Vanilla
Yellow Petrolatum	Petrolatum
Yellow Precipitate	Yellow Mercuric Oxide
Yerba Santa	Eriodictyon
Yerba Santa Fluidextract	Eriodictyon Fluidextract
Zinc Compounds and Eugenol Cement	Zinc-Eugenol Cement

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† Inclusion of a name in this list does not signify any official recognition or relation to a substance or preparation in this National Formulary. This list is intended only for convenient reference and identification of substances or preparations when they are sought for under formerly used names.

* Official title in NF XII.

** USP XVII article admitted to NF XIII.

Equivalents of Weights and Measures

Metric, Avoirdupois and Apothecaries

NOTE: These values are for water at the temperature of 4° C. (39.2° F.) in vacuum. For practical purposes the values may be used without correction.

This table of exact equivalents should not be confused with the table of *approximate* dose equivalents which appears on the inside of the back cover. The latter table is provided only as a convenience to physicians for prescribing.

For the conversion of specific quantities in converting pharmaceutical formulas, use the exact equivalents. For prescription compounding, use the exact equivalents rounded to three significant figures.

Weights						Metric Weight and Measure	Measures		
Grains	Apothecaries oz.	Apothecaries grains	Avoirdupois lb.	Avoirdupois oz.	Avoirdupois grains	g. or ml.	Fluid oz.	Fluid minims	Decimal Equivalent
15432.4	32	72.4	2	3	119.9	**1000**	33	391.1	33.815
14604.1	30	204.1	2	1	166.6	946.333	**32**	....	32
14000.0	29	80.0	**2**	..	....	907.185	30	324.6	30.676
7716.2	16	36.2	1	1	278.7	**500**	16	435.6	16.907
7302.1	15	102.1	1	..	302.1	473.167	**16**	....	16
7000.0	14	280.0	**1**	..	....	453.592	15	162.3	15.338
5760.0	**12**	...	..	13	72.5	373.242	12	298.1	12.621
3840.0	**8**	....	..	8	340.0	248.828	8	198.7	8.414
3651.0	7	291.0	..	8	151.0	236.583	**8**	....	8
3500.0	7	140.0	..	**8**	....	226.796	7	321.1	7.669
3086.5	6	206.5	..	7	24.0	**200**	6	366.2	6.763
1920.0	**4**	...	..	4	170.0	124.414	4	99.4	4.207
1825.5	3	385.5	..	4	75.5	118.292	**4**	....	4
1750.0	3	310.0	..	**4**	....	113.398	3	400.6	3.835
1543.2	3	103.2	..	3	230.7	**100**	3	183.1	3.381
960.0	**2**	...	..	2	85.0	62.207	2	49.7	2.104
912.8	1	432.8	..	2	37.8	59.146	**2**	....	2
875.0	1	395.0	..	**2**	....	56.699	1	440.3	1.917
771.6	1	291.6	..	1	334.1	**50**	1	331.5	1.691
480.0	**1**	...	..	1	42.5	31.1035	1	24.9	1.052
456.380	..	...	..	1	18.88	29.5729	**1**	....	1
437.5	..	...	..	**1**	....	28.350	..	460.15	0.959
385.8	..	...	..	..	....	**25**	..	405.78	0.845
308.6	..	...	..	..	....	**20**	..	324.62	0.676
154.3	..	...	..	..	....	**10**	..	162.31	0.338
19.02	..	...	..	..	....	1.232	..	**20**	....
15.4324	..	...	..	..	....	**1**	..	16.23	....
9.51	..	...	..	..	....	0.616	..	**10**	....
4.75	..	...	..	..	....	0.308	..	**5**	....
1	..	...	..	..	....	0.06480	..	1.0517	....

Metric Equivalents of Grains (5 Grains and Less)

Grains	Milligrams	Grains	Milligrams	Grains	Milligrams
5	324	1/2	32.4	1/30	2.2
4	259	2/5	25.9	1/40	1.6
3	194	1/4	16.2	1/50	1.3
2	130	1/8	8.1	1/60	1.1
1 1/2	97	1/10	6.5	1/64	1.0
1	65	1/16	4.0	1/100	0.6
3/4	48.6	1/20	3.2	1/128	0.5

Alcoholometric Table*

Percentage of C_2H_5OH		Specific Gravity in Air		Percentage of C_2H_5OH		Specific Gravity in Air	
By Volume at 15.56° C. (1)	By Weight (2)	At $\frac{25^\circ}{25^\circ}$ (3)	At $\frac{15.56^\circ}{15.56^\circ}$ (4)	By Weight (5)	By Volume at 15.56° (6)	At $\frac{25^\circ}{25^\circ}$ (7)	At $\frac{15.56^\circ}{15.56^\circ}$ (8)
0	0.00	1.0000	1.0000	0	0.00	1.0000	1.0000
1	0.80	0.9985	0.9985	1	1.26	0.9981	0.9981
2	1.59	0.9970	0.9970	2	2.51	0.9963	0.9963
3	2.39	0.9956	0.9956	3	3.76	0.9945	0.9945
4	3.19	0.9941	0.9942	4	5.00	0.9927	0.9928
5	4.00	0.9927	0.9928	5	6.24	0.9911	0.9912
6	4.80	0.9914	0.9915	6	7.48	0.9894	0.9896
7	5.61	0.9901	0.9902	7	8.71	0.9879	0.9881
8	6.42	0.9888	0.9890	8	9.94	0.9863	0.9867
9	7.23	0.9875	0.9878	9	11.17	0.9848	0.9852
10	8.05	0.9862	0.9866	10	12.39	0.9833	0.9839
11	8.86	0.9850	0.9854	11	13.61	0.9818	0.9825
12	9.68	0.9838	0.9843	12	14.83	0.9804	0.9812
13	10.50	0.9826	0.9832	13	16.05	0.9789	0.9799
14	11.32	0.9814	0.9821	14	17.26	0.9776	0.9787
15	12.14	0.9802	0.9810	15	18.47	0.9762	0.9774
16	12.96	0.9790	0.9800	16	19.68	0.9748	0.9763
17	13.79	0.9778	0.9789	17	20.88	0.9734	0.9751
18	14.61	0.9767	0.9779	18	22.08	0.9720	0.9738
19	15.44	0.9756	0.9769	19	23.28	0.9706	0.9726
20	16.27	0.9744	0.9759	20	24.47	0.9692	0.9714
21	17.10	0.9733	0.9749	21	25.66	0.9677	0.9701
22	17.93	0.9721	0.9739	22	26.85	0.9663	0.9688
23	18.77	0.9710	0.9729	23	28.03	0.9648	0.9675
24	19.60	0.9698	0.9719	24	29.21	0.9633	0.9662
25	20.44	0.9685	0.9708	25	30.39	0.9617	0.9648
26	21.29	0.9673	0.9697	26	31.56	0.9601	0.9635
27	22.13	0.9661	0.9687	27	32.72	0.9585	0.9620
28	22.97	0.9648	0.9676	28	33.88	0.9568	0.9605
29	23.82	0.9635	0.9664	29	35.03	0.9551	0.9590
30	24.67	0.9622	0.9653	30	36.18	0.9534	0.9574
31	25.52	0.9609	0.9641	31	37.32	0.9516	0.9558
32	26.38	0.9595	0.9629	32	38.46	0.9498	0.9541
33	27.24	0.9581	0.9617	33	39.59	0.9480	0.9524
34	28.10	0.9567	0.9604	34	40.72	0.9461	0.9506
35	28.97	0.9552	0.9590	35	41.83	0.9442	0.9488
36	29.84	0.9537	0.9576	36	42.94	0.9422	0.9470
37	30.72	0.9521	0.9562	37	44.05	0.9402	0.9451
38	31.60	0.9506	0.9548	38	45.15	0.9382	0.9432
39	32.48	0.9489	0.9533	39	46.24	0.9362	0.9412
40	33.36	0.9473	0.9517	40	47.33	0.9341	0.9392
41	34.25	0.9456	0.9501	41	48.41	0.9320	0.9372
42	35.15	0.9439	0.9485	42	49.48	0.9299	0.9352
43	36.05	0.9421	0.9469	43	50.55	0.9278	0.9331
44	36.96	0.9403	0.9452	44	51.61	0.9256	0.9310
45	37.87	0.9385	0.9434	45	52.66	0.9235	0.9289

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* Based upon data appearing in the National Bureau of Standards Bulletin, vol. 9, pp. 424–5.

Alcoholometric Table—(concluded)

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
46	38.78	0.9366	0.9417	46	53.71	0.9213	0.9268
47	39.70	0.9348	0.9399	47	54.75	0.9191	0.9246
48	40.62	0.9328	0.9380	48	55.78	0.9169	0.9225
49	41.55	0.9309	0.9361	49	56.81	0.9147	0.9203
50	42.49	0.9289	0.9342	50	57.83	0.9124	0.9181
51	43.43	0.9269	0.9322	51	58.84	0.9102	0.9159
52	44.37	0.9248	0.9302	52	59.85	0.9079	0.9137
53	45.33	0.9228	0.9282	53	60.85	0.9056	0.9114
54	46.28	0.9207	0.9262	54	61.85	0.9033	0.9092
55	47.25	0.9185	0.9241	55	62.84	0.9010	0.9069
56	48.21	0.9164	0.9220	56	63.82	0.8987	0.9046
57	49.19	0.9142	0.9199	57	64.80	0.8964	0.9024
58	50.17	0.9120	0.9177	58	65.77	0.8941	0.9001
59	51.15	0.9098	0.9155	59	66.73	0.8918	0.8978
60	52.15	0.9076	0.9133	60	67.69	0.8895	0.8955
61	53.15	0.9053	0.9111	61	68.64	0.8871	0.8932
62	54.15	0.9030	0.9088	62	69.59	0.8848	0.8909
63	55.17	0.9006	0.9065	63	70.52	0.8824	0.8886
64	56.18	0.8983	0.9042	64	71.46	0.8801	0.8862
65	57.21	0.8959	0.9019	65	72.38	0.8777	0.8839
66	58.24	0.8936	0.8995	66	73.30	0.8753	0.8815
67	59.28	0.8911	0.8972	67	74.21	0.8729	0.8792
68	60.33	0.8887	0.8948	68	75.12	0.8706	0.8768
69	61.38	0.8862	0.8923	69	76.02	0.8682	0.8745
70	62.44	0.8837	0.8899	70	76.91	0.8658	0.8721
71	63.51	0.8812	0.8874	71	77.79	0.8634	0.8697
72	64.59	0.8787	0.8848	72	78.67	0.8609	0.8673
73	65.67	0.8761	0.8823	73	79.54	0.8585	0.8649
74	66.77	0.8735	0.8797	74	80.41	0.8561	0.8625
75	67.87	0.8709	0.8771	75	81.27	0.8537	0.8601
76	68.98	0.8682	0.8745	76	82.12	0.8512	0.8576
77	70.10	0.8655	0.8718	77	82.97	0.8488	0.8552
78	71.23	0.8628	0.8691	78	83.81	0.8463	0.8528
79	72.38	0.8600	0.8664	79	84.64	0.8439	0.8503
80	73.53	0.8572	0.8636	80	85.46	0.8414	0.8479
81	74.69	0.8544	0.8608	81	86.28	0.8389	0.8454
82	75.86	0.8516	0.8580	82	87.08	0.8364	0.8429
83	77.04	0.8487	0.8551	83	87.89	0.8339	0.8404
84	78.23	0.8458	0.8522	84	88.68	0.8314	0.8379
85	79.44	0.8428	0.8493	85	89.46	0.8288	0.8354
86	80.66	0.8397	0.8462	86	90.24	0.8263	0.8328
87	81.90	0.8367	0.8432	87	91.01	0.8237	0.8303
88	83.14	0.8335	0.8401	88	91.77	0.8211	0.8276
89	84.41	0.8303	0.8369	89	92.52	0.8184	0.8250
90	85.69	0.8271	0.8336	90	93.25	0.8158	0.8224
91	86.99	0.8237	0.8303	91	93.98	0.8131	0.8197
92	88.31	0.8202	0.8268	92	94.70	0.8104	0.8170
93	89.65	0.8167	0.8233	93	95.41	0.8076	0.8142
94	91.03	0.8130	0.8196	94	96.10	0.8048	0.8114
95	92.42	0.8092	0.8158	95	96.79	0.8020	0.8086
96	93.85	0.8053	0.8118	96	97.46	0.7992	0.8057
97	95.32	0.8011	0.8077	97	98.12	0.7962	0.8028
98	96.82	0.7968	0.8033	98	98.76	0.7932	0.7988
99	98.38	0.7921	0.7986	99	99.39	0.7902	0.7967
100	100.00	0.7871	0.7936	100	100.00	0.7871	0.7936

Thermometric Equivalents

Centigrade (Celsius) to Fahrenheit Scales

$$\frac{9}{5}\,°\,\text{C.} + 32 = °\,\text{F.}$$

° C.	° F.	° C.	° F.	° C.	° F.	° C.	° F.	° C.	° F.
−20	−4.0	21	69.8	61	141.8	101	213.8	141	285.8
−19	−2.2	22	71.6	62	143.6	102	215.6	142	287.6
−18	−0.4	23	73.4	63	145.4	103	217.4	143	289.4
−17	1.4	24	75.2	64	147.2	104	219.2	144	291.2
−16	3.2	25	77.	65	149.	105	221.	145	293.
−15	5.	26	78.8	66	150.8	106	222.8	146	294.8
−14	6.8	27	80.6	67	152.6	107	224.6	147	296.6
−13	8.6	28	82.4	68	154.4	108	226.4	148	298.4
−12	10.4	29	84.2	69	156.2	109	228.2	149	300.2
−11	12.2	30	86.	70	158.	110	230.	150	302.
−10	14.	31	87.8	71	159.8	111	231.8	151	303.8
− 9	15.8	32	89.6	72	161.6	112	233.6	152	305.6
− 8	17.6	33	91.4	73	163.4	113	235.4	153	307.4
− 7	19.4	34	93.2	74	165.2	114	237.2	154	309.2
− 6	21.2	35	95	75	167.	115	239.	155	311.
− 5	23.	36	96.8	76	168.8	116	240.8	156	312.8
− 4	24.8	37	98.6	77	170.6	117	242.6	157	314.6
− 3	26.6	38	100.4	78	172.4	118	244.4	158	316.4
− 2	28.4	39	102.2	79	174.2	119	246.2	159	318.2
− 1	30.2	40	104.	80	176.	120	248.	160	320.
0	32.	41	105.8	81	177.8	121	249.8	161	321.8
1	33.8	42	107.6	82	179.6	122	251.6	162	323.6
2	35.6	43	109.4	83	181.4	123	253.4	163	325.4
3	37.4	44	111.2	84	183.2	124	255.2	164	327.2
4	39.2	45	113.	85	185.	125	257.	165	329.
5	41.	46	114.8	86	186.8	126	258.8	166	330.8
6	42.8	47	116.6	87	188.6	127	260.6	167	332.6
7	44.6	48	118.4	88	190.4	128	262.4	168	334.4
8	46.4	49	120.2	89	192.2	129	264.2	169	336.2
9	48.2	50	122.	90	194.	130	266.	170	338.
10	50.	51	123.8	91	195.8	131	267.8	171	339.8
11	51.8	52	125.6	92	197.6	132	269.6	172	341.6
12	53.6	53	127.4	93	199.4	133	271.4	173	343.4
13	55.4	54	129.2	94	201.2	134	273.2	174	345.2
14	57.2	55	131.	95	203.	135	275.	175	347.
15	59.	56	132.8	96	204.8	136	276.8	176	348.8
16	60.8	57	134.6	97	206.6	137	278.6	177	350.6
17	62.6	58	136.4	98	208.4	138	280.4	178	352.4
18	64.4	59	138.2	99	210.2	139	282.2	179	354.2
19	66.2	60	140.	100	212.	140	284.	180	356.
20	68.								

Thermometric Equivalents—(concluded)

Fahrenheit to Centigrade (Celsius) Scales

$$(^\circ\text{F.} - 32) \times \frac{5}{9} = {}^\circ\text{C.}$$

° F.	° C.	° F.	° C.	° F.	° C.	° F.	° C.	° F.	° C.
0	−17.78	51	10.56	101	38.33	151	66.11	201	93.89
1	−17.22	52	11.11	102	38.89	152	66.67	202	94.44
2	−16.67	53	11.67	103	39.44	153	67.22	203	95.
3	−16.11	54	12.22	104	40.	154	67.78	204	95.56
4	−15.56	55	12.78	105	40.56	155	68.33	205	96.11
5	−15.	56	13.33	106	41.11	156	68.89	206	96.67
6	−14.44	57	13.89	107	41.67	157	69.44	207	97.22
7	−13.89	58	14.44	108	42.22	158	70.	208	97.78
8	−13.33	59	15.	109	42.78	159	70.56	209	98.33
9	−12.78	60	15.56	110	43.33	160	71.11	210	98.89
10	−12.22	61	16.11	111	43.89	161	71.67	211	99.44
11	−11.67	62	16.67	112	44.44	162	72.22	212	100.
12	−11.11	63	17.22	113	45.	163	72.78	213	100.56
13	−10.56	64	17.78	114	45.56	164	73.33	214	101.11
14	−10.	65	18.33	115	46.11	165	73.89	215	101.67
15	− 9.44	66	18.89	116	46.67	166	74.44	216	102.22
16	− 8.89	67	19.44	117	47.22	167	75.	217	102.78
17	− 8.33	68	20.	118	47.78	168	75.56	218	103.33
18	− 7.78	69	20.56	119	48.33	169	76.11	219	103.89
19	− 7.22	70	21.11	120	48.89	170	76.67	220	104.44
20	− 6.67	71	21.67	121	49.44	171	77.22	221	105.
21	− 6.11	72	22.22	122	50.	172	77.78	222	105.56
22	− 5.56	73	22.78	123	50.56	173	78.33	223	106.11
23	− 5.	74	23.33	124	51.11	174	78.89	224	106.67
24	− 4.44	75	23.89	125	51.67	175	79.44	225	107.22
25	− 3.89	76	24.44	126	52.22	176	80.	226	107.78
26	− 3.33	77	25.	127	52.78	177	80.56	227	108.33
27	− 2.78	78	25.56	128	53.33	178	81.11	228	108.89
28	− 2.22	79	26.11	129	53.89	179	81.67	229	109.44
29	− 1.67	80	26.67	130	54.44	180	82.22	230	110.
30	− 1.11	81	27.22	131	55.	181	82.78	231	110.56
31	− 0.56	82	27.78	132	55.56	182	83.33	232	111.11
32	0.	83	28.33	133	56.11	183	83.89	233	111.67
33	0.56	84	28.89	134	56.67	184	84.44	234	112.22
34	1.11	85	29.44	135	57.22	185	85.	235	112.78
35	1.67	86	30.	136	57.78	186	85.56	236	113.33
36	2.22	87	30.56	137	58.33	187	86.11	237	113.89
37	2.78	88	31.11	138	58.89	188	86.67	238	114.44
38	3.33	89	31.67	139	59.44	189	87.22	239	115.
39	3.89	90	32.22	140	60.	190	87.78	240	115.56
40	4.44	91	32.78	141	60.56	191	88.33	241	116.11
41	5.	92	33.33	142	61.11	192	88.89	242	116.67
42	5.56	93	33.89	143	61.67	193	89.44	243	117.22
43	6.11	94	34.44	144	62.22	194	90.	244	117.78
44	6.67	95	35.	145	62.78	195	90.56	245	118.33
45	7.22	96	35.56	146	63.33	196	91.11	246	118.89
46	7.78	97	36.11	147	63.89	197	91.67	247	119.44
47	8.33	98	36.67	148	64.44	198	92.22	248	120.
48	8.89	99	37.22	149	65.	199	92.78	249	120.56
49	9.44	100	37.78	150	65.56	200	93.33	250	121.11
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TABLE OF RELATIVE ATOMIC WEIGHTS

Recommended by the International Commission on Atomic Weights (1967)

Name	Symbol	Atomic Number	Atomic Weight[c]
Actinium	Ac	89	(227)
Aluminum	Al	13	26.9815
Americium	Am	95	(243)
Antimony	Sb	51	121.75
Argon	Ar	18	39.948
Arsenic	As	33	74.9216
Astatine	At	85	(210)
Barium	Ba	56	137.34
Berkelium	Bk	97	(247)
Beryllium	Be	4	9.0122
Bismuth	Bi	83	208.980
Boron	B	5	10.811[a]
Bromine	Br	35	79.904[b]
Cadmium	Cd	48	112.40
Calcium	Ca	20	40.08
Californium	Cf	98	[252]
Carbon	C	6	12.01115[a]
Cerium	Ce	58	140.12
Cesium	Cs	55	132.905
Chlorine	Cl	17	35.453[b]
Chromium	Cr	24	51.996
Cobalt	Co	27	58.9332
Copper	Cu	29	63.546[b]
Curium	Cm	96	(247)
Dysprosium	Dy	66	162.50
Einsteinium	Es	99	(254)
Erbium	Er	68	167.26
Europium	Eu	63	151.96
Fermium	Fm	100	(257)
Fluorine	F	9	18.9984
Francium	Fr	87	(223)
Gadolinium	Gd	64	157.25
Gallium	Ga	31	69.72
Germanium	Ge	32	72.59
Gold	Au	79	196.967
Hafnium	Hf	72	178.49
Helium	He	2	4.0026
Holmium	Ho	67	164.930
Hydrogen	H	1	1.00797[a]
Indium	In	49	114.82
Iodine	I	53	126.9044
Iridium	Ir	77	192.2
Iron	Fe	26	55.847[b]
Krypton	Kr	36	83.80
Lanthanum	La	57	138.91
Lawrencium	Lr	. . .	(256)
Lead	Pb	82	207.19
Lithium	Li	3	6.939
Lutetium	Lu	71	174.97
Magnesium	Mg	12	24.305
Manganese	Mn	25	54.9380
Mendelevium	Md	101	(257)
Mercury	Hg	80	200.59
Molybdenum	Mo	42	95.94
Neodymium	Nd	60	144.24
Neon	Ne	10	20.179[b]
Neptunium	Np	93	(237)
Nickel	Ni	28	58.71
Niobium	Nb	41	92.906
Nitrogen	N	7	14.0067
Nobelium	No	102	(255)
Osmium	Os	76	190.2
Oxygen	O	8	15.9994[a]
Palladium	Pd	46	106.4
Phosphorus	P	15	30.9738
Platinum	Pt	78	195.09
Plutonium	Pu	94	(244)
Polonium	Po	84	[210]
Potassium	K	19	39.102
Praseodymium	Pr	59	140.907
Promethium	Pm	61	[147]
Protactinium	Pa	91	(231)
Radium	Ra	88	(226)
Radon	Rn	86	(222)
Rhenium	Re	75	186.2
Rhodium	Rh	45	102.905
Rubidium	Rb	37	85.47
Ruthenium	Ru	44	101.07
Samarium	Sm	62	150.35
Scandium	Sc	21	44.956
Selenium	Se	34	78.96
Silicon	Si	14	28.086[a]
Silver	Ag	47	107.868[b]
Sodium	Na	11	22.9898
Strontium	Sr	38	87.62
Sulfur	S	16	32.064[a]
Tantalum	Ta	73	180.948
Technetium	Tc	43	[99]
Tellurium	Te	52	127.60
Terbium	Tb	65	158.924
Thallium	Tl	81	204.37
Thorium	Th	90	232.038
Thulium	Tm	69	168.934
Tin	Sn	50	118.69
Titanium	Ti	22	47.90
Tungsten	W	74	183.85
Uranium	U	92	238.03
Vanadium	V	23	50.942
Xenon	Xe	54	131.30
Ytterbium	Yb	70	173.04
Yttrium	Y	39	88.905
Zinc	Zn	30	65.37
Zirconium	Zr	40	91.22

[a] Atomic weights so designated are known to be variable because of natural variations in isotopic composition. The observed ranges are: Hydrogen ±0.00001, Boron ±0.003, Carbon ±0.00005, Oxygen ±0.0001, Silicon ±0.001, Sulfur ±0.003.

[b] Atomic weights so designated are believed to have the following experimental uncertainties: Chlorine ±0.001, Copper ±0.001, Iron ±0.003, Bromine ±0.001, Neon ±0.003, Silver ±0.001.

[c] Based on the atomic mass of $^{12}C = 12$. Values in parentheses are for selected radioactive isotopes of longest known half-life; those in brackets are for isotopes that are better known than the corresponding isotopes of the longest half-life.

Pocket Inside Front Cover

National Formulary XIII

Interim Revision Announcements and Supplements

The need for continuously refining specifications and updating standards has become increasingly urgent. This development has been a natural consequence of the introduction of many new drugs and the accelerated growth of our knowledge concerning the pharmaceutical sciences.

In order to keep the National Formulary abreast of these developments and to maintain its standards as current as practicable, the NF Board from time to time issues Interim Revision Announcements and Supplements.

Interim Revision Announcements to this edition of the National Formulary may be issued in the form of releases to the pharmaceutical press. Such Announcements are designed to publicize promptly minor corrections and other revisions of limited scope. Reprints of Interim Revision Announcements will be made available only upon request accompanied by an addressed and stamped envelope.

Supplements to NF XIII, covering a wider scope than can be included adequately in Interim Revision Announcements, will also be issued when necessary. Interim Revision Announcements published prior to the issuance of a Supplement will be incorporated in the Supplement. Supplements, when issued, will be published and their availability publicized as described in the preceding paragraph. Copies will be mailed automatically, without cost, to every owner of a National Formulary XIII who takes the precaution to fill in and mail the "order form" postal card which is inserted between this page and the inside back cover.

All correspondence relating to Supplements should be addressed to the National Formulary, American Pharmaceutical Association, 2215 Constitution Avenue, N.W., Washington, DC 20037

TABLE OF METRIC DOSES WITH APPROXIMATE APOTHECARY EQUIVALENTS

The *approximate* dose equivalents in the following table represent the quantities usually prescribed, under identical conditions, by physicians trained, respectively, in the metric or in the apothecary system of weights and measures. In labeling dosage forms in both the metric and the apothecary systems, if one is the approximate equivalent of the other, the approximate figure shall be enclosed in parentheses.

When prepared dosage forms such as tablets, capsules, pills, etc., are prescribed in the metric system, the pharmacist may dispense the corresponding *approximate* equivalent in the apothecary system, and vice versa, as indicated in the following table.

NOTE: For the conversion of specific quantities in a prescription which requires compounding, or in converting a pharmaceutical formula from one system of weights or measures to the other, *exact* equivalents must be used (see page 965).

Liquid Measure

Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents
1000 ml.	1 quart	3 ml.	45 minims
750 ml.	$1\frac{1}{2}$ pints	2 ml.	30 minims
500 ml.	1 pint	1 ml.	15 minims
250 ml.	8 fluidounces	0.75 ml.	12 minims
200 ml.	7 fluidounces	0.6 ml.	10 minims
100 ml.	$3\frac{1}{2}$ fluidounces	0.5 ml.	8 minims
50 ml.	$1\frac{3}{4}$ fluidounces	0.3 ml.	5 minims
30 ml.	1 fluidounce	0.25 ml.	4 minims
15 ml.	4 fluidrams	0.2 ml.	3 minims
10 ml.	$2\frac{1}{2}$ fluidrams	0.1 ml.	$1\frac{1}{2}$ minims
8 ml.	2 fluidrams	0.06 ml.	1 minim
5 ml.	$1\frac{1}{4}$ fluidrams	0.05 ml.	$\frac{3}{4}$ minim
4 ml.	1 fluidram	0.03 ml.	$\frac{1}{2}$ minim

Weight

Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents
30 g.	1 ounce	30 mg.	$\frac{1}{2}$ grain
15 g.	4 drams	25 mg.	$\frac{3}{8}$ grain
10 g.	$2\frac{1}{2}$ drams	20 mg.	$\frac{1}{3}$ grain
7.5 g.	2 drams	15 mg.	$\frac{1}{4}$ grain
6 g.	90 grains	12 mg.	$\frac{1}{5}$ grain
5 g.	75 grains	10 mg.	$\frac{1}{6}$ grain
4 g.	60 grains (1 dram)	8 mg.	$\frac{1}{8}$ grain
3 g.	45 grains	6 mg.	$\frac{1}{10}$ grain
2 g.	30 grains ($\frac{1}{2}$ dram)	5 mg.	$\frac{1}{12}$ grain
1.5 g.	22 grains	4 mg.	$\frac{1}{15}$ grain
1 g.	15 grains	3 mg.	$\frac{1}{20}$ grain
750 mg.	12 grains	2 mg.	$\frac{1}{30}$ grain
600 mg.	10 grains	1.5 mg.	$\frac{1}{40}$ grain
500 mg.	$7\frac{1}{2}$ grains	1.2 mg.	$\frac{1}{50}$ grain
400 mg.	6 grains	1 mg.	$\frac{1}{60}$ grain
300 mg.	5 grains	800 mcg.	$\frac{1}{80}$ grain
250 mg.	4 grains	600 mcg.	$\frac{1}{100}$ grain
200 mg.	3 grains	500 mcg.	$\frac{1}{120}$ grain
150 mg.	$2\frac{1}{2}$ grains	400 mcg.	$\frac{1}{150}$ grain
120 mg.	2 grains	300 mcg.	$\frac{1}{200}$ grain
100 mg.	$1\frac{1}{2}$ grains	250 mcg.	$\frac{1}{250}$ grain
75 mg.	$1\frac{1}{4}$ grains	200 mcg.	$\frac{1}{300}$ grain
60 mg.	1 grain	150 mcg.	$\frac{1}{400}$ grain
50 mg.	$\frac{3}{4}$ grain	120 mcg.	$\frac{1}{500}$ grain
40 mg.	$\frac{2}{3}$ grain	100 mcg.	$\frac{1}{600}$ grain

NOTE: One milliliter (ml.) is used herein as the equivalent of 1 cubic centimeter (cc.); 1 ml. is exactly equivalent to 1.000028 cc.

In dispensing practice, a solution of approximately 1 percent weight in volume may be prepared by dissolving 4.5 grains of a solid in sufficient of the solvent to make 1 fluidounce of the solution; a solution of approximately 1 percent volume in volume by dissolving 4.8 minims of a liquid in sufficient of the solvent to make 1 fluidounce of the solution.

The above approximate dose equivalents have been adopted by the National Formulary and the US Pharmacopeia, and these dose equivalents have the approval of the federal Food and Drug Administration.